
Identification of Blood Glucose Patterns through Continuous Glucose Monitoring and Decision Trees



Trabajo de Fin de Grado en Ingeniería Informática

Francisco José Lozano Serrano

Dirigido por

José Ignacio Hidalgo Pérez

Departamento de Arquitectura de Computadores y Automática

Facultad de Informática

Universidad Complutense de Madrid

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Francisco José Lozano Serrano

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Science

Directed by

José Ignacio Hidalgo Pérez

Computer Architecture and Automation Department
Computer Science Faculty
Complutense University of Madrid

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Abstract

The demand for Continuous Glucose Monitoring (CGM) systems is increasing among type 1 diabetic patients. Some companies are trying to improve the monitorization and the usability of these systems. One example is Abbott FreeStyle Libre, which provides a new concept of glucose monitoring called Flash Glucose Monitoring (FGM). FGM is more affordable and does not need calibration. This increased demand for these devices means an opportunity for data and computer scientists, who can contribute to the development of decision-making support systems based on the data collected from the devices.

Type 1 diabetic patients that use FreeStyle Libre must enter the number of insulin and carbohydrates units that they are going to take before a meal. Using both the entered data and the blood glucose values collected by the device automatically, the application developed in this project generates a report of the patient's glucose patterns. In addition, it provides a web application that allows the user to upload the data obtained from his device and download the report on his computer or smartphone.

The application uses decision trees to detect the patterns and entails a starting point in the creation of ensemble models with more predictive power, also based on decision trees. Furthermore, the methodology makes a segmentation of the data set in blocks, determined by the different meals done throughout the day, adding more information to the set of variables used to train the model. As a result, the application can discover repetitive patterns in the daily life of the patient, which can help him to take early preventive measures for risk situations in a period close to the next meal.

Key words: Diabetes, Decision Trees, Glucose Monitoring, Patterns

Resumen

La demanda de sistemas de Monitorización Continua de Glucosa (CGM) está aumentando entre los pacientes diabéticos de tipo 1. Algunas empresas tratan de mejorar la monitorización y la usabilidad de estos sistemas. Un ejemplo es Abbott FreeStyle Libre, que proporciona un nuevo concepto en monitorización de glucosa llamado Monitorización Flash de Glucosa (FGM). FGM es más asequible y no requiere calibración. El aumento de demanda de estos dispositivos significa una oportunidad para informáticos y científicos de datos, que pueden contribuir al desarrollo de sistemas de apoyo a la toma de decisiones basado en los datos recogidos por estos dispositivos.

Los pacientes diabéticos de tipo 1 que usan FreeStyle libre, deben introducir los datos de insulina y carbohidratos antes de cada comida. Usando los datos introducidos por los pacientes y los niveles de glucosa recogidos automáticamente por el dispositivo, la aplicación desarrollada en este proyecto es capaz de generar un informe de patrones de glucosa del paciente. Además, se proporciona una aplicación web que permite al usuario subir los datos obtenidos del dispositivo y descargarse el informe en su propio ordenador o dispositivo móvil.

La aplicación hace uso de árboles de decisión para detectar los patrones y supone un punto de partida en la elaboración de modelos ensamblados con mayor poder predictivo, también basados en árboles de decisión. Además, la metodología segmenta el conjunto de datos en bloques marcado por las diferentes comidas del día, añadiendo información adicional al conjunto de variables usadas para entrenar el modelo. Como resultado, la aplicación es capaz de describir patrones repetitivos en la vida diaria del paciente, que le pueden ayudar a anticiparse a una situación de riesgo en un periodo de tiempo próximo a la siguiente comida.

Palabras clave: Diabetes, Árboles de decisión, Monitorización de glucosa, Patrones.

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Chapter 1

Introduction

Diabetes mellitus is a disease that is characterised by the presence of hyperglycemia as a consequence of defects in insulin secretion, insulin action or both (Diaz Aguilar y Mézcua Navarro, 2007).

Diabetes mellitus can be classified into four different types:

- Diabetes mellitus type 1, which causes the destruction of a beta cell that is present in the pancreas, and an absolute deficiency in insulin production.
- Diabetes mellitus type 2, which causes resistance to the insulin action and certain deficiency in the insulin secretion.
- Other types of diabetes, related to genetic defects that affect to the beta cell such as pancreatic lesions, drugs and other factors.
- Gestational diabetes, which appears during the gestation period.

It is estimated that one to five percent of the Spanish population suffers from diabetes mellitus type 1 (Soriguer et al., 2012). Although this kind of diabetes is not related to the lifestyle, its incidence is increasing among the population. Diabetics must take an insulin dose before or shortly after each meal to keep their blood glucose level in harmless range. Many tools allow diabetic patients to monitor their blood glucose values in real time and have a better control of their disease.

The increment in the commercialization of blood glucose monitoring systems is an opportunity for data and computer scientists to create innovative tools that help diabetics to anticipate to upcoming risk situations and improve their lifestyle. It is important to provide them with a service that detect repetitive risky situations, but it is even more important to give them meaningful answers according to these patterns. This last guidance must be by thoroughly designed by means of a joint effort among computer scientist and

physicians, who are responsible for giving a correct characterization to the identified patterns.

This project aims to provide a decision-making support system to type 1 diabetic patients. The application uses the data obtained from an FGM (Flash glucose monitoring) device. The main difference with traditional CGM (Continuous glucose monitoring) devices is that the patient does not see his blood sugar levels until he scans the sensor with the reader. Another difference is that the device does not need to be calibrated whilst some other CGM devices need to be calibrated several times per day (Heinemann y Freckmann, 2015).

The patient has access to a report of patterns of his blood glucose values by uploading the data of the reader to a web application. This idea has been inspired by other studies and applications focused on the development of a solution for diabetic people using data from a monitoring system.

One example of an application developed for diabetics is glUCModel, a monitoring and modelling system for chronic diseases applied to diabetes (Hidalgo et al., 2014). This application allows doctors to consult the information of their patients and have better control over their illness. Moreover, glUCModel offers a recommendation system that provides automatic recommendations to their patients, increasing their awareness of their condition. This project has a similar goal, but using a different approach through decision trees to recognise the patterns and segmenting each day in blocks determined by the meals.

Another study that has provided some ideas to this project has been described in (Wiley, 2011). This thesis presents a support system to diabetics using data from a CGM device and machine learning techniques, which try to predict the blood glucose values of the patients. This study contains interesting contributions about data preprocessing, feature engineering, classification of glycemic variability and evaluation techniques.

In the following subsections, the motivation, the objectives and the structure of the document are described.

1.1. Motivation

Currently, many different models try to predict the blood glucose values of diabetic patients and warn them when these values are not in a safe range. However, these models often act like black boxes that send alerts, but do not provide an explanation regarding their provenance. Furthermore, the patient sometimes has a greater need of knowing how to react to frequent dangerous situations that compromise his health. Once the patient becomes aware of these patterns, he is able to modify his daily habits to avoid unwanted scenarios.

Detecting patterns in blood glucose levels is a challenge that we wanted

to face with this project. Giving a useful and accessible description to both patients and physicians is even more challenging. It is necessary to innovate to address these challenges and provide solutions potentially helpful. However, innovation and willingness are not sufficient if they are not coupled with the creation of realistic scenarios using actual data. Working with data collected from diabetic patients is something that made this project very attractive to us because accessing to real information is often limited or restricted.

Data-driven solutions are a trend in the last years due to the existence of tens of data mining and big data tools to discover hidden patterns in large datasets. This project was an opportunity to turn our ideas into action and use our knowledge in data science to improve the life quality of diabetics. Further, we wanted to contribute to the research of new methods of prevention of hyperglycemia . We believe that computer scientists have the social responsibility of providing solutions to society problems using the available technology. Developing this application is only one small contribution to a collective effort of helping diabetics to live as normal a life as possible.

1.2. Objectives

The primary purpose of this project is to develop a Python package that generates reports using data files obtained from FreeStyle Libre, a blood glucose monitoring device. To enhance this package, we had as secondary objective to develop a web application that integrated the package and offered its services to the user through a web browser.

The main package is not intended to be a predictive tool for the patient but rather a descriptive instrument to support decision making. The application is not connected in real time to another device or smartphone, but it uses the data files obtained by the patient from the reader. Despite these limitations, another objective of the application is still being useful for the patient.

Finally, and according to the open source and multiplatform philosophy of Python, the ultimate objective is to contribute to an active community that is looking for new models and creating decision-making support systems to help diabetic people and physicians. Therefore, the project is available on GitHub and works in Windows and Linux operating systems that can run Python and *conda* environments. This ensures that other researchers can use the software, either through the Python package or the web application, and get new ideas about data preprocessing and the use of decision trees in the creation of models of blood glucose.

1.3. Document structure

This document follows a structure that consists of the following chapters:

In **Chapter 1**, we introduce the project, describing its motivation and objectives that defined the guidelines of the development process. In **Chapter 2**, we describe the materials and methods that allowed us to work on this project. Firstly, the device in charge of monitoring the blood glucose values and secondly, the decision trees used to create the model, explaining their features and the algorithm they use.

Chapter 3 explains the design of both the application core and the web application that wraps the core. This chapter also includes the structure of classes, the flow chart and some details about the used technology.

Chapter 4 describes the whole methodology from the beginning, when the application reads the data files and process them, to the creation of the model and the generation of the report.

In **Chapter 5** shows the results of applying the methodology in a series of data files, commenting the relevant ones and discussing which were expected beforehand.

Finally, **Chapter 6** contains a conclusion and suggests new ideas for a possible improvement of the methodology.

Chapter 2

Introducción

La diabetes mellitus es una enfermedad caracterizada por la presencia de hiperglucemia como consecuencia de defectos en la secreción de insulina, la acción de insulina, o ambas (Díaz Aguilar y Mézcua Navarro, 2007).

La diabetes mellitus puede ser clasificada en cuatro tipos diferentes:

1. Diabetes mellitus tipo 1, que causa la destrucción de una célula beta que está presente en el páncreas, y una absoluta deficiencia en la producción de insulina.
2. Diabetes mellitus tipo 2, que causa resistencia a la acción de la insulina y cierta deficiencia en la secreción de insulina.
3. Otros tipos de diabetes, relacionadas con defectos genéticos que afectan a la célula beta tales como lesiones pancreáticas, drogas y otros factores.
4. Diabetes gestacional, que aparece durante el periodo de gestación.

Se estima que entre el uno y el cinco por ciento de la población española sufre de diabetes mellitus tipo 1 (Soriguer et al., 2012). Aunque este tipo de diabetes no está relacionada con el estilo de vida, su incidencia está aumentando entre la población. Los diabéticos deben administrarse una dosis de insulina antes o poco después de cada comida para mantener sus valores de glucosa en sangre en un rango no dañino para su salud. Muchas herramientas permiten a los pacientes diabéticos monitorizar sus valores de glucosa en sangre en tiempo real y tener un mejor control sobre su enfermedad.

El incremento en la comercialización de sistemas de monitorización de glucosa es una oportunidad que se presenta a científicos de datos e informáticos para crear herramientas innovadoras que ayuden a los diabéticos a anticiparse a situaciones de riesgo próximas y mejorar su estilo de vida. Es importante proveerles de un servicio que detecte situaciones de riesgo repetitivas, pero es aún más importante darles respuestas significativas de

acuerdo a esos patrones. Esta última orientación debe ser minuciosamente diseñada por medio de un esfuerzo conjunto entre informáticos y médicos, responsables de dar una correcta caracterización a los patrones identificados.

Este proyecto aspira a proporcionar un sistema de apoyo a la toma de decisiones a pacientes diabéticos de tipo 1. La aplicación usa data obtenida de un dispositivo FGM (Monitorización de glucosa Flash), La principal diferencia con los dispositivos CGM (Monitorización continua de glucosa) es que el paciente no ve sus niveles de glucosa en sangre hasta que él escanea el sensor con el lector. Otra diferencia es que el dispositivo no necesita ser calibrado mientras que otros dispositivos CGM necesita ser calibrados varias veces por día (Heinemann y Freckmann, 2015).

El paciente tiene acceso al informe de patrones de sus niveles de glucosa en sangre subiendo los datos del lector a una aplicación web. Esta idea ha sido inspirada por otros estudios y aplicaciones enfocados en el desarrollo de una solución para personas diabética usando datos de un sistema de monitorización.

Un ejemplo de una aplicación desarrollada para diabéticos es glUCModel, un sistema de monitorización y modelado de enfermedades crónicas aplicado a la diabetes (Hidalgo et al., 2014). Esta aplicación permite a los doctores consultar la información de sus pacientes y tener un mejor control sobre su enfermedad. Además, glUCModel ofrece un sistema de recomendación que proporciona recomendaciones automáticas a sus pacientes, aumentando la concienciación sobre su enfermedad. Este proyecto tiene un objetivo similar, pero usando un enfoque diferente a través de árboles de decisión para reconocer los patrones y segmentando cada día en bloques determinados por cada comida.

Otro estudio que ha aportado algunas ideas a este proyecto ha sido descrito en (Wiley, 2011). Esta tesis presenta un sistema de apoyo a los diabéticos usando datos de un dispositivo CGM y técnicas de aprendizaje automático, que tratan de predecir los valores de glucosa en sangre de los pacientes. Este estudio contiene contribuciones interesantes sobre preprocesamiento de datos, ingeniería de factores, clasificación de la variabilidad glucémica y técnicas de evaluación.

2.1. Motivación

En la actualidad, diferentes modelos tratan de predecir los niveles de glucosa de pacientes diabéticos y avisarles cuando estos valores no están en un rango seguro. Sin embargo, estos modelos a menudo actúan como cajas negras que envían alertas, pero no proporcionan una explicación sobre su origen. Además, el paciente a veces tiene una necesidad mayor de saber cómo reaccionar a situaciones frecuentes de riesgo, que ponen en peligro su salud. Una vez el paciente es consciente de estos patrones, es capaz de

modificar sus hábitos diarios para evitar escenarios indeseados.

Detectar patrones en los niveles de glucosa en la sangre es un reto al que quisimos hacer frente con este proyecto. Dar una descripción útil y accesible a pacientes y médicos supone un reto aún mayor. Es necesario innovar para atajar estos desafíos y proporcionar soluciones potencialmente útiles. Sin embargo, la innovación y la predisposición no son suficientes si ellos no van ligados con la creación de contextos realistas usando datos reales. Trabajar con los datos recogidos de pacientes diabéticos es algo que hizo este proyecto muy interesante para nosotros ya que el acceso a la información real está a menudo limitada o restringida.

Las soluciones basadas en datos son una tendencia en los últimos años debido a la existencia de decenas de herramientas de minería de datos y *big data* que descubren patrones en conjuntos de datos muy grandes. Este proyecto fue una oportunidad para poner en práctica nuestras ideas y usar nuestro conocimiento en ciencia de datos para mejorar la calidad de vida de los diabéticos. Además, quisimos contribuir a la investigación de nuevos métodos en la prevención de la hiperglucemia. Creemos que los informáticos tenemos la responsabilidad social de proporcionar soluciones a los problemas de la sociedad usando la tecnología disponible. Desarrollar esta aplicación es solo una pequeña contribución a un esfuerzo colectivo de ayudar a los diabéticos a tener una vida lo más normal posible.

2.2. Objetivos

El objetivo principal de este proyecto es desarrollar un paquete de Python que genere informes usando ficheros de datos obtenidos de FreeStyle Libre, un dispositivo de monitorización de glucosa. Para mejorar este paquete, tuvimos como objetivo secundario desarrollar una aplicación que integrara y ofreciera sus servicios al usuario a través de un navegador web.

El paquete principal no pretende ser una herramienta de predicción para el paciente, sino un instrumento descriptivo para el apoyo en la toma de decisiones. La aplicación no está conectada en tiempo real a otro dispositivo móvil, pero usa los ficheros de datos obtenidos por el paciente del lector. A pesar de estas limitaciones, otro objetivo de la aplicación es ser aun así útil para el paciente.

Finalmente, y de acuerdo a la filosofía de código abierto y multiplataforma de Python, el objetivo final es contribuir a una comunidad activa que está buscando nuevos modelos y crear sistemas de apoyo a la toma de decisiones para ayudar a pacientes diabéticos y médicos. Por lo tanto, este proyecto está disponible en GitHub y trabaja en sistemas operativos Windows y Linux que sean capaces de ejecutar Python y entornos *conda*. Esto asegura que otros investigadores pueden usar el software, sea a través del paquete Python o de la aplicación web, y adquirir nuevas ideas sobre pre-

procesamiento de datos y el uso de árboles de decisión en la creación de modelos de glucosa.

2.3. Estructura del documento

Este documento sigue una estructura compuesta de los siguientes capítulos:

1. En el capítulo **1** presentamos el proyecto, describiendo su motivación y los objetivos que definen las directrices del proceso de desarrollo.
2. En el **capítulo 2** describimos los materiales y métodos que nos han permitido trabajar en este proyecto. En primer lugar, el dispositivo encargado de la monitorización de los valores de glucosa en sangre, y en segundo lugar, los árboles de decisión usados para crear el modelo, explicando sus características y el algoritmo que usan.
3. El **capítulo 3** explica el diseño de el núcleo de la aplicación y la aplicación web que lo envuelve. Este capítulo también contiene la estructura de clases, el diagrama de flujo y algunos detalles sobre la tecnología usada.
4. El **capítulo 4** describe la metodología completa desde el principio, cuando la aplicación lee los ficheros de datos y los procesa, hasta la creación del modelo y la generación del informe.
5. En el **capítulo 5** mostramos los resultados de aplicar la metodología en una serie de ficheros de datos, comentando los más relevantes y comentando cuales eran esperados de antemano.
6. Finalmente, el **capítulo 6** contiene una conclusión y sugiere nuevas ideas para una posible mejora de la metodología

Chapter 3

Materials and methods

3.1. FreeStyle Blood Glucose Monitoring System

The data files that are processed in this project were obtained from FreeStyle Libre devices, provided by the company Abbott Diabetes Care, which sells several appliances for glucose control by diabetic patients. Continuous glucose monitoring (CGM) became available in the year 2000, having a measurement error of more than $\pm 20\%$. New devices have reduced this error 10 %, but there is a continuous effort for reducing this margin by the producers (Rodbard, 2016).

FreeStyle Libre is an an interstitial glucose monitoring system, which is an alternative for the capillary and venous blood glucose measurement (Bailey et al., 2015). One advantage of this kind of devices is that it provides more reference points of measurement than conventional blood glucose devices, which makes them an interesting source of data to create a model.

The reader captures the data from the sensor when it is closer than 4 cm, and the patient can get his blood glucose values at any moment by reading the data from the sensor. The patient must synchronise the data with the sensor at least once each 8 hours. If not, the sensor erases all the information until the patient does a new synchronisation. On the other hand, the reader can keep blood glucose values for 90 days and provide data through the sensor that is easy to interpret by the patient.

The patients can obtain the data files by connecting the device to a PC. Ten patients provided twelve data files to test the application. The data files were anonymized before their analysis, leaving only the initials of the patients as an identifier. Some of the data files were incomplete or suffered from a lack of data that had to be considered and managed by the application. The quality of the datafiles and the results obtained are discussed in chapter 6.

The data files obtained from a FreeStyle reader contained the following columns:



Figura 3.1: FreeStyle Libre – Image from Wikimedia Commons – CC BY-SA 4.0

- ID of the row
- Date and time that indicates when the record was taken
- Type of register. The type of registers can take the following values:
 - 0: Automatic glucose value register, saved each 15 minutes by the device.
 - 1: Manual blood glucose value register, saved in the record after a read by the patient.
 - 2: Register of insulin without a numeric value.
 - 3: Register of carbohydrates without a numeric value.
 - 4: Register of insulin done with a numeric value.
 - 5: Register of carbohydrates with a numeric value.
- Blood glucose value in rows with register type 0 (mg/dl).

- Blood glucose value in rows with register type 1 (mg/dl).
- Rapid insulin register without a numeric value in rows with register type 2.
- Carbohydrates without a numeric value in rows with register type 3
- Units of rapid insulin entered by the patient in rows with register type 4.
- Units of carbohydrates entered by the patient in rows with register type 5.

The carbohydrates and the insulin values (either rapid or slow insulin dose) must be entered by the patient manually before a meal. Other columns such as slow insulin units or data from finger stick were not included in any of the data files analysed for this project, and they were not considered in the data preprocessing procedure.

3.2. Decision Trees

Decision tree learning is a supervised learning technique to do classification instances using a series of variables (referred as attributes) (van der Aalst, 2016). One of the variables must be used as a categorical variable to label the data and the result of the learning process is organised in form of a tree. The purpose of the model is to predict the outcome of the label of a new set of examples by following the rules created by the training examples in the tree.

The implementation of the decision tree classifier used in this project is the one included in the library *scikit-learn*, a package that contains several tools for data mining and data analysis in Python. This classifier is implemented in the class *DecisionTreeClassifier* and can perform multi-class classification on a data set (dec, 2016).

Given a matrix X of m examples with n features and a label vector Y , a decision tree splits the instances into subsets recursively such that the examples with the same label are grouped as members of the same class. The impurity in one node of the decision tree is computed using an impurity function, which differs depending on the problem to be solved (Either a classification or a regression problem). The measure of impurity used in this application is the Gini Index, explained in (Tan et al., 2006) and (Madigan y Curet, 2006).

Let t be a node of the decision tree, the Gini Index of a node t is defined as:

$$\text{GINI}(t) = 1 - \sum_j [p(j|t)]^2$$

Where $p(j|t)$ is the proportion of observations of class j in node t

For example, for a decision tree focused on detecting hypoglycemia patterns like the one in Figure 5.6, the root node contains the following examples:

- Examples classified as “No Hyperglycemia Diagnosis Next Block” (\overline{H}): 638
- Examples classified as “Hyperglycemia Diagnosis Next Block” (H): 1375

This means that:

$$P(H) = \frac{1375}{1375 + 638} = \frac{1375}{2013}, \quad P(\overline{H}) = \frac{638}{1375 + 638} = \frac{638}{2013}$$

Thus, the Gini Index is calculated as follows:

$$\text{GINI}(t) = 1 - P(H)^2 - P(\overline{H})^2 = 1 - \left(\frac{1375}{2013}\right)^2 - \left(\frac{638}{2013}\right)^2 = 0,433$$

Now, let t be a node of the decision tree and s split for t :

- P_R is the proportion of examples at node t that are included in the right child node t_R and $i(t_R)$ is the impurity of the right child node.
- P_L is the proportion of examples at node t that are included in the left child node t_L and $i(t_L)$ is the impurity of the left child node.

The reduction of Gini impurity (*Gini-Gain*) for a node t and a split s is defined as:

$$\Delta i(s, t) = i(t) - P_L i(t_L) - P_R i(t_R)$$

The purpose of the decision tree is to choose the rule in each node that minimises the impurity for that node and repeating the procedure in its child nodes until the maximum depth of the tree is reached. There are several algorithms that try to find the best set of rules to minimise the impurity. The one used by the *DecisionTreeClassifier* is an optimisation of the CART (Classification and Regression Trees) algorithm. CART-based decision trees follow three main steps (Madigan y Curet, 2006):

1. Choose the children nodes of each node with less impurity than the parent node.
2. Prune the branches and nodes according to split quality criteria or when the tree is complete.
3. Assign predicted class to the terminal nodes that according to the number examples with greater representation.

Some of the reasons why I have chosen decision trees for this project are the following ones:

- They are easy to understand and interpret, acting like a white box model. The user can find an explanation for each of the rules included in the tree looking at the Boolean logic. This feature fulfils the requirement of using a white box model. Compared to other models such as convolutional neural networks, whose behaviour is difficult to explain to the user, the decisions made by the tree are easily identifiable .
- Decision-tree learners tend to overfit the data if the number of features is very high, but this is not the case of this project, which only uses 22 features for training the model.
- The cost of constructing a decision tree using the efficient implementation of *scikit-learn* is $\mathcal{O}(n_{features}n_{samples}\log(n_{samples}))$ and the cost of predict data is $\mathcal{O}(\log(n_{samples}))$. The cost-complexity pruning method of CART makes it a fast algorithm for data interpretation, which follows the purpose of the application of being a descriptive tool rather than a predictive tool (Lim et al., 2000).
- Finding an optimal decision tree is an NP-complete problem and the different implementations use heuristic algorithms to construct them. This flaw is mitigated using ensemble approaches but this option is not considered for this project because they are harder to explain with simple rules. However, finding an optimal tree is not crucial in this application because its main purpose is to find general and repetitive patterns which can be descriptive enough even if the splits are not optimal.

An example code that uses the `DecisionTreeClassifier` can be found in Appendix A. This example code loads one of the data files provided for this study and takes the automatic blood glucose registers (Register type 5) to define the following labels: Hypoglycemia, hyperglycemia or in range. After defining the labels, the two features used for training the classifier are the prior and subsequent blood glucose values to the current one. These two features are obtained by shifting the column one \pm one period. The purpose of the classifier is to identify the label that corresponds to the current blood glucose value considering only the prior and subsequent blood glucose values, which were taken 15 minutes before/after.

Figure 3.2 shows the effect of modifying the maximum depth of the tree to control the overfitting. Geometrically, we can observe in the different subplots that the decision trees decompose the attribute space into disjoint subsets using decision rules that are orthogonal to the attribute axes (?). This rectangular partitioning of the attribute space is a flaw of the decision

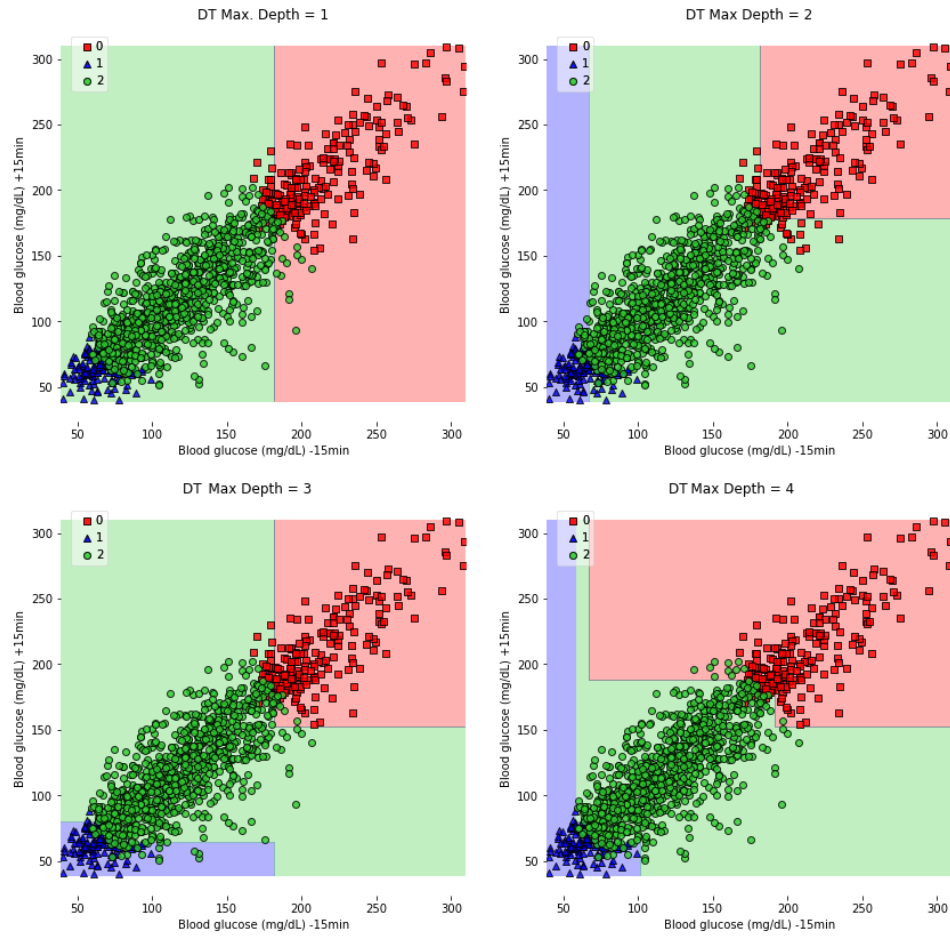


Figure 3.2: Plot of decision areas in decision trees with maximum depth limit of 1, 2, 3 and 4 levels. The three numbers of the legend stand for Hyperglycemia, Hypoglycemia and ‘In range’ situations

trees as it does not handle correlated features precisely. Also, pruning the decision tree is necessary, not only because of overfitting control but also because the trees can grow to large dimensions if the number of used features are very high.

Chapter 4

Design of the application

The development of the application was split into two phases. The purpose of the first step was to develop a self-contained package that could be used both through the Python interpreter or by a web application. The second phase of the application was developing a web application that allowed a user to upload a series of data files and obtain the report from a browser. In the two following sections, we explain the design, the requirements and the technology used for these two modules.

4.1. Application core

This main requirement for the application core was to generate a PDF file using a series of data files obtained from a FreeStyle device. The core is purely written in Python, and it uses *pandas* as the main library to upload and manipulate the data. The package contains a sub package with the classes of the application and two extra modules that include all the preprocessing and data visualisation functionalities. The classes that model the logic of the application are the following ones:

- **Model:** The main features of a Model object are to preprocess the data, make the main dataset available to the three decision trees, and bring them together to work as a single model that recognise a series of patterns. These patterns are obtained from *DecisionTree* objects, and they are used to generate the report in the *generate_report* method.
- **DecisionTree:** The *DecisionTree* class encapsulates the *DecisionTreeClassifier* objects of the *sklearn* library and provide some extra functionalities like obtaining a series of patterns, reading the tree structure and creating *Pattern* objects or exporting an image of the tree.
- **Pattern:** The main attribute of the class *Pattern* is a list of *Rule* objects that define the pattern. Also, it includes some statistics related to

the number of samples of each class and its impurity. One important function is `__str__`, the built-in function of Python that can be overwritten to define the string that represents the object. This function returns a human-readable version of the pattern that is displayed in the reports.

- **Rule:** This class only encapsulates three attributes: A feature, an operator and a threshold value. It also contains some support functions that are used by the `__str__` to create the string representation of the class.
- **Translator:** The class translator contains two bidirectional dictionaries (*bidict*) that allow establishing one-to-one mappings between two variables efficiently. These dictionaries include the internal representation of the variables in the program and its translation to the corresponding language. The *Translator* class translates the headers of the source files to its internal representation and all the variables that are written in the report.

All the described classes and their relations can be observed in Figure 4.1. The support modules are the following ones:

- **preprocessor.py:** The preprocessor contains all the functions necessary to transform the raw data into a dataset that can be passed to the decision trees. It carries out the validation of periods and the division of the data set in blocks. It also cleans the data, generates new columns and binarizes the labels.
- **visualization.py:** This module has functions that generate plots and images that are included in the report such as the blood glucose values or the representation of the decision trees. It also has functions that support the generation of plots like smoothing the curves of the plots.
- **report.py:** A module that allows generating a report from the command line with a series of arguments.

4.2. Web application

The web application has been built using the *Django* Framework, written in Python. This framework lets the user define the model of your application and forget about the interaction with the database thanks to its ORM (*Object-Relational Mapping*). It provides automatic generation of formulas and it has a good interface to build templates. Also, it contains a series of modules that reduces development time and increase the security.

One of the packages included in the web application is the core package of the project, described in the previous section. The core is completely integrated into the web application because it does not require a communication protocol since it is also developed in Python. The user needs to fulfil two requirements before starting to use the application:

1. The user must sign up and enter some personal data: His name, his email and a password. After this step, he must log in with his account to have access to the service of the application. This authentication protocol has been implemented using the authentication system of Django, which handles user accounts and permissions while preserving security.
2. The user must accept a document of terms and conditions of the application. These conditions imply to relinquish some data that it is used by the application to generate the reports. This mechanism has been implemented using the module *Django-termsandconditions*, and it allows to define the terms and conditions from the administration. It also keeps version control of the conditions, forcing a user to accept the terms again if they are updated.

When a logged user accepts the terms and conditions, the application records his IP address and the date of acceptance, giving him access to the service.

Through the web interface, the user can upload and delete a series of data files obtained from his FreeStyle devices. It also contains some buttons to select which of the features must be used for training the model and some additional features of the reports like defining the language or including information about the blocks. Figure 4.2 shows the interface of the page that the user access to generate the report.

Once the user clicks the button “Generate report”, it sends a POST request to the server. The time necessary to produce the report may vary depending on the resources of the host server and the number of data files that the application must process. After the application core has generated the PDF file, it is returned as a response, and the user can visualise it on the browser or download it to his file system.

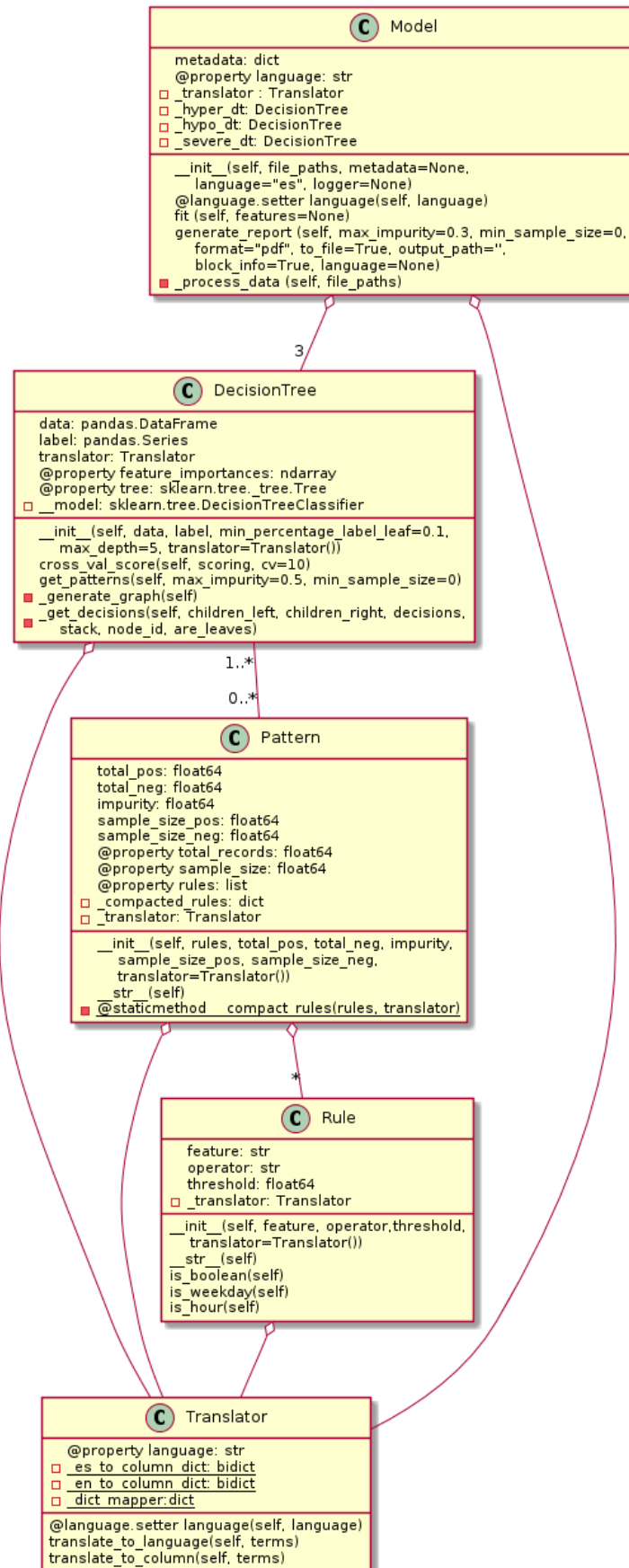


Figura 4.1: Class diagram of the core application

The screenshot shows the 'Glycemic Patterns' web application interface. At the top, there is a header bar with the application name 'Glycemic Patterns' on the left, a 'Generate report' button in the center, and a user profile icon labeled 'DPE' on the right. A vertical 'b1d1' logo is positioned on the far right. The main content area is divided into several sections: 1. 'Report generation' section. 2. 'Upload the text files obtained from your device' section, which includes a file list with one item 'DPE_20160520_20160803_FREE_STYLE.txt - Delete' and a 'Choose File' button. 3. A file selection area with a 'Choose File' button and the text 'No file chosen', and an 'UPLOAD' button. 4. 'Select the glucose variables that you have available' section, featuring five buttons: 'MEAN', 'STANDARD DEVIATION', 'MAXIMUM', 'MINIMUM', and 'MAGE'. 5. 'Select the language of the report' section, with two buttons: 'ENGLISH' and 'ESPAÑOL'. 6. 'Configure other settings of the report' section, containing an 'INCLUDE INFORMATION OF DAYS AND BLOCKS' button and a prominent green 'GENERATE REPORT' button at the bottom.

Glycemic Patterns Generate report DPE

Report generation

Upload the text files obtained from your device

- DPE_20160520_20160803_FREE_STYLE.txt - Delete

Choose File No file chosen

UPLOAD

Select the glucose variables that you have available

MEAN STANDARD DEVIATION MAXIMUM MINIMUM MAGE

Select the language of the report

ENGLISH ESPAÑOL

Configure other settings of the report

INCLUDE INFORMATION OF DAYS AND BLOCKS

GENERATE REPORT

Figura 4.2: Web interface used by the user to generate a report

Chapter 5

Methodology

5.1. Introduction

The application core has been designed to work as an independent component which can be used as a standalone application or as part of an outer application like the web application developed in this project.

The main input of the application core is a series of data files that are used for training the model, and that can be obtained directly from a FreeStyle Libre device. Also, the application provides the possibility of specifying the source language of the data file and some configuration parameters of the decision trees. The output is a report that contains the blood glucose patterns, the decision trees used to extract them and some additional information related to the blood glucose values of the patient. This report can be exported both in PDF and HTML format. In the following sections, we describe the different steps of the program flow (See Figure 5.1)

5.2. Data preprocessing

The data preprocessing process starts reading a data file (or a set of data files). The *Model* object uses the preprocessing module to deal with the raw data and build the main data set of the patient. The main data set is composed of every preprocessed data file and it is used as a single data frame to train the model. This object accepts a list of file paths and the language of the data files' headers to identify each column. It creates a *Translator* object, in charge of translating the columns to the syntax used inside the code to select the columns.

In the next step, the program iterates all the data files, preprocessing and adding each of them to the main data set. If the format is not the one expected (Different headers, corruption of the data file, wrong extension, etc.), it raises a *DataFormatException*, which can be handled by the web

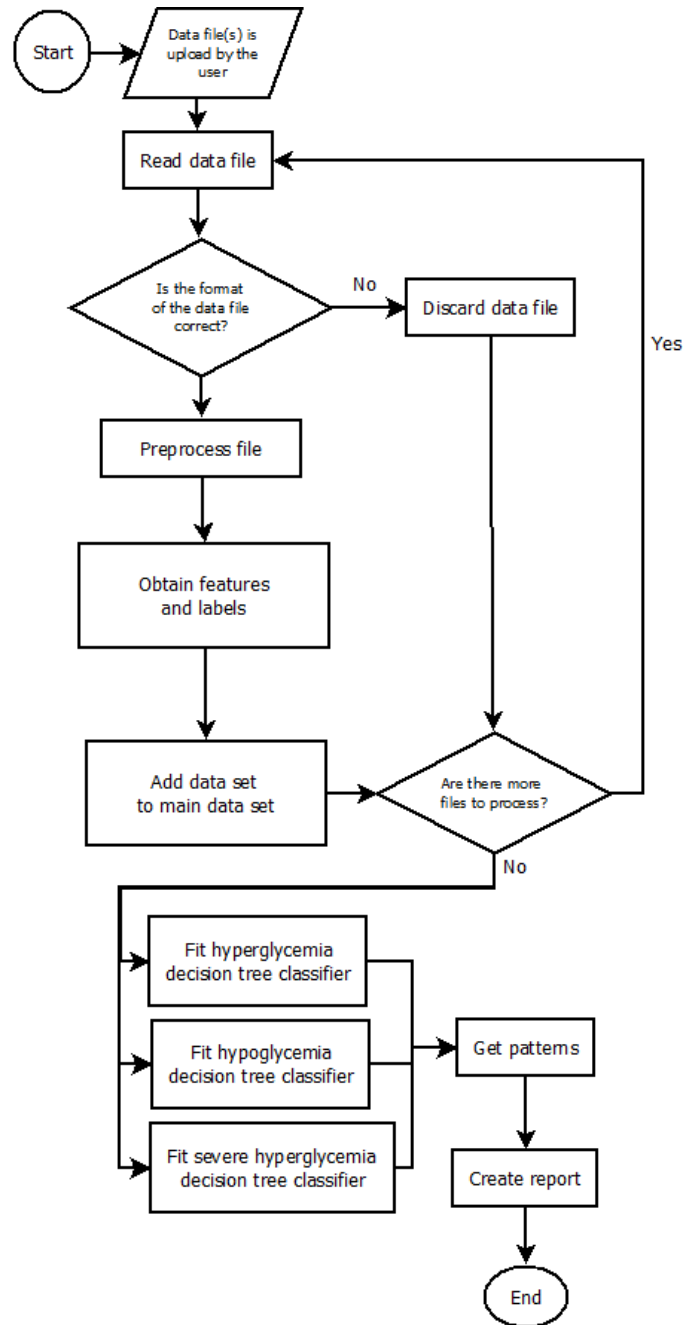


Figura 5.1: Main flowchart of the application methodology

application and reported to the user.

The information in the data files comes from the values recorded by the device, which means that the noise is also encoded in the blood glucose

values. The most common anomalies in the data collected by blood glucose monitoring systems appear when the device becomes uncalibrated. Although FreeStyle Libre devices do not need to be calibrated, they have an estimation error that can not be corrected with information obtained from any external source (such as finger sticks). Other CGM devices provide the possibility of entering external data to calibrate them, which can be used to detect and fix the anomalies in the recorded values. We made the assumption that the estimation error of the sensor is propagated to the patterns extracted by the model.

The three most important preprocessing techniques used to treat each data file are missing data management, the definition of blocks and smoothing of blood glucose curves.

5.2.1. Dealing with missing data

One of the main issues of the FreeStyle device is that it deletes all the entries in the last 8 hours if the patient do not synchronise the reader with the sensor in that period. As a consequence, the data file may contain some discontinuities in the data. In the application, these gaps are handled dividing one data file in a subset of valid periods. The definition of a valid period is a period of no more than 8 hours without carbohydrate registers. This definition is necessary because some features (like the time elapsed since the last meal) are calculated considering the period between two meals. If this period is too large (Greater than 8 hours) because of missing data, it introduces some noise in the data set that may decrease the accuracy of the model.

Once each period is defined, they are preprocessed separately and incorporated to the main dataset. In any of the following cases, the program discards a period:

- If it has no carbohydrates registers
- Its duration is less than 24 hours.
- It results in an empty set after preprocessing it.

Another drawback is that the information of meals is only available from one single source: The input made by the patient in the device. If the patient does not specify the number of carbohydrates, it assigns one by default. However, if the patient does not enter any carbohydrate data, this data is not available in the dataset. Some data such as the meal time cannot be inferred easily because a patient typically does not eat at the same time every day. The patient should provide accurate and realistic information so that the report can reveal if carbohydrates have any impact on the patient's blood glucose values.

If some carbohydrate data are missing, it causes a poor division of the day in blocks and, therefore, decrease the quality of the dataset and the patterns. This issue is notified in the program as a warning (and reflected in the report subsequently) when the mean of carbohydrates of each day in the period is less than one per day.

5.2.2. Define blocks

Each day of the patient is divided into a series of blocks defined by the different meals that the patient has throughout the day. A time window from two hours before to four hours later is defined for each carbohydrate entry (register type number 5), and it only includes automatic measurement of blood glucose values (register type number 1). Each block also contains the number of insulin doses that the patient has taken in the block. The column that contains the number of carbohydrates units and the column without numerical value of carbohydrates units in a meal (one unit) are merged. This intersection is also made for the columns that contains the values of rapid insulin doses taken by the patient before a meal.

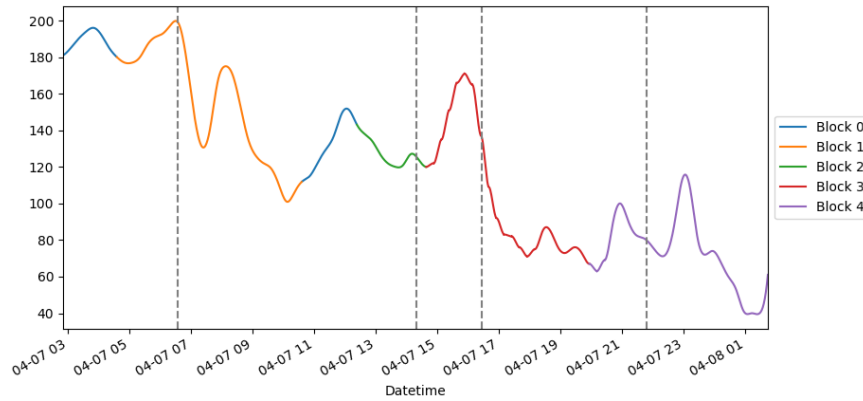


Figura 5.2: Division in blocks of a sample day. Some blocks are overlapped.

The next step entails iterating all the days of the dataset and define their corresponding blocks from 0 to n (Block 0 is the block associated with all entries that have not been included in any other block). For each day, all the occurrences of carbohydrates of that day are used to define its time window and include all the values of carbohydrates and rapid insulin that correspond to that block.

Therefore, several blocks may reference to the same doses of carbohydrates and insulin due to a possible overlapping between blocks. The pre-processor considers this overlapping and it unfolds every overlapped entry in several entries, indicating in one new feature that the block is overlapped

Datetime	Glucose Auto	Block	Day Block	Overlapped Block	Carbo Block	Rapid Insulin Block
05/04/2016 7:46	97	1	05/04/2016	FALSE	1	1
05/04/2016 8:01	94	1	05/04/2016	FALSE	1	1
05/04/2016 8:16	83	1	05/04/2016	FALSE	1	1
05/04/2016 8:31	74	1	05/04/2016	TRUE	1	1
05/04/2016 8:31	74	2	05/04/2016	TRUE	1	0
05/04/2016 8:46	74	1	05/04/2016	TRUE	1	1
05/04/2016 8:46	74	2	05/04/2016	TRUE	1	0

Table 5.1: Unfolding of registers with overlapped blocks

5.2.3. Smoothing curves

Capillary measurements allow a maximum error of 15 % for glucose levels ≥ 100 mg/dL and ± 15 mg/dL for glucose levels < 100 mg/dL (Fokkert et al., 2017). Even though CGM sensors are useful tools in the management of diabetes due to their high accuracy (Mastrototaro et al., 2008), these errors must be considered by their users. For example, a physician usually smooths the blood glucose values implicitly when he analyses the data.

This technique is used by the program when the visualisation module creates the daily plots included in the report. Cubic spline smoothing is one technique that many physicians identify as the one that is more similar to the implicit smoothing that they apply when they analyse a time series of blood glucose values (Wiley, 2011). Cubic spline smoothing is a cubic spline interpolation that uses a regularisation parameter, and it is described in (Pollock, 1993). I used the implementation that *pandas* library includes, which is a wrapper of the method *interp1d*, present in package *interpolate*, which belongs to the library *scipy*.

One feature of the cubic spline smoothing technique that we could not use is the possibility of giving extra weighting to some register values rather than others. Other devices allow entering finger stick data, which is more reliable than the automatic measurement, and more weight is usually assigned to this kind of registers. A FreeStyle Libre device does not support to enter external data and therefore the algorithm treats all the blood glucose values of the time series equally.

5.3. Define features and labels

After preprocessing all the valid periods and add them to the main dataset, the process of feature engineering starts. One of the constraints of

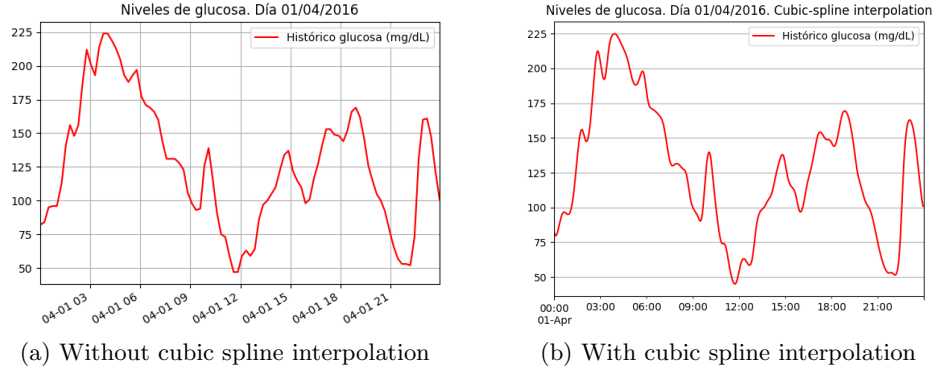


Figura 5.3: Comparison of plots with/without cubic spline interpolation

this project is that the physician and the patient must obtain easily the information of the features used for training the models so that they can understand the patterns and take preventive measures in the future . Many machine learning models are trained using a lot of different features obtained from the time series and complex formulas that increase the predictive power of the model but reduces its comprehensibility drastically.

This application not only uses features that are easy to obtain by the user, but also it allows to select the desired features that will be used to obtain the patterns. Table 5.2 details a summary of the features that can be used to train the model.

One of the main factors that have a high influence in the appearance of blood glucose disorders is the glycemic variability (Monnier y Colette, 2008). One of the main concerns of the Type-1 diabetic patients is to control their blood glucose values as much as possible. Despite there is no universally accepted metric to measure glycemic variability, Monnier and Colette state that MAGE (Mean Amplitude of Glycemic Excursion) is an appropriate measure.

MAGE is obtained by calculating the arithmetic mean of all the differences of peak-to-nadir excursions that are greater than the standard deviation of the day. Figure 5.4 shows one 24-hour period of one sample taken from the FreeStyle device. The module used to obtain the peaks was *peakdetect*.

The standard deviation of this period is 44.57, and the first excursion that is greater than the standard deviation starts at 4 am. In total, there are six different excursions that are greater than the standard deviation. To obtain the MAGE, we sum them up and divide by 6. The result is the following one:

$$\frac{131 + 46 + 92 + 122 + 117 + 109}{6} = 102,83333$$

Feature	Description
G	Value of blood glucose (mg/dL) of the record
G_{D-1}	Value of blood glucose (mg/dL) one day before the record
ΔG_{D-1}	Difference between the value of blood glucose one day before the record and the value of blood glucose of the record (mg/dL)
B	Block number of the record (0-n).
H	Hour (0-23) of the record
OL_B	The block of the record is overlapped (True/False)
WD	Day of the week of the record (0-6)
Δt_{LM}	Elapsed minutes since the last meal until the record (0-n)
H_{LM}	Hour of the last meal before the record (0-23)
μ_{B-1}	Mean of the blood glucose values of the previous block to the record
σ_{B-1}	Standard deviation of the blood glucose values of the previous block to the record
max_{B-1}	Maximum value of the blood glucose values of the previous block to the record
min_{B-1}	Minimum value of the blood glucose values of the previous block to the record
car_{B-1}	Carbohydrates (portions) of the previous block to the record
in_{B-1}	Rapid-acting insulin (units) of the previous block to the record
μ_{D-1}	Mean of the blood glucose values of the previous day to the record
σ_{D-1}	Standard deviation of the blood glucose values of the previous day to the record
max_{D-1}	Maximum value of the blood glucose values of the previous day to the record
min_{D-1}	Minimum value of the blood glucose values of the previous day to the record
car_{D-1}	Carbohydrates (portions) of the previous block to the record
in_{D-1}	Rapid-acting insulin (units) of the previous block to the record
$MAGE_{D-1}$	Mean Amplitude of Glycemic Excursion of the previous day

Table 5.2: Features used in training process and their descriptions

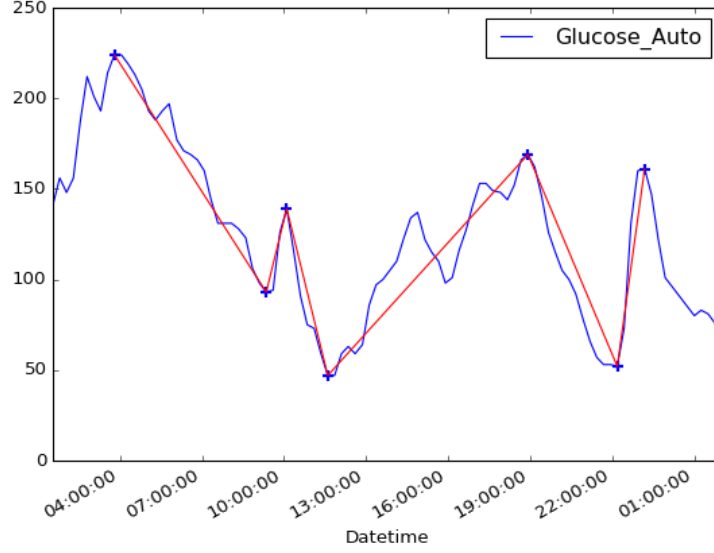


Figure 5.4: Peak detection and excursions to calculate the MAGE

The information that the patient must have at a certain moment was a constraint to define the features. Therefore, the methodology does not include some features that contain information which is derived from periods that finishes after the record time. For example, the number of blocks of each day was not included as a feature because if it is 4 pm and the patient has made three meals until then, he may not know how many meals will take until going to sleep. This problem is stressed if the patient varies the number of meals depending on his blood glucose values. Hence, the included features contain information that is available to the patient at any moment such as the blood glucose values of the previous block or the previous day or the day of the week.

Some features need to be adjusted, inferred or removed after the calculation because they are not directly available from the data. One case is $D - 1$ (Value of blood glucose one day before the record), which needs to be rounded to the nearest quarter hour to get G_{D-1} as the register taken twenty four hours before may not exist due to a shifting in the measurement time. After this adjustment, ΔG_{D-1} can be obtained safely.

The function removes the records with no previous meal, with no data of the previous block or that does not contain values of glucose of the previous day after adding new features to the dataset. These records usually correspond to the first records of the dataset. Once these rows are deleted,

Datetime	G	B	Diagnosis	Hyper-glycemia Diagnosis	Hypo-glycemia Diagnosis	In-Range Diagnosis	Severe Hyper-glycemia Diagnosis
01/04/2016 20:56	78	4	In Range	0	0	1	0
01/04/2016 21:11	66	4	Hypo-glycemia	0	1	0	0
02/04/2016 17:50	233	4	Hyper-glycemia	1	0	0	0
02/04/2016 18:05	249	4	Severe Hyper-glycemia	1	0	0	1

Table 5.3: Mapping of the diagnosis labels

the following features are inferred with the mean of the column.

Finally, the function in charge of the feature engineering process defines the labels. Firstly, it adds one column with the diagnosis of the record using the blood glucose value. The four possible diagnoses are the following ones:

1. Hypoglycemia: If $G < 70$ mg/dL
2. In range: If $70 \text{ mg/dL} \leq G \leq 180 \text{ mg/dL}$
3. Hyperglycemia: If $G > 180$ mg/dL
4. Severe hyperglycemia: If $G > 240$ mg/dL

It is important to highlight that the hyperglycemia and severe hyperglycemia labels are overlapped when $G > 240$ mg/dL. This overlapping is considered in the next step when the labels are binarized. Binarizing the labels consist in create a binary column for every label and each of these columns is used by a different decision tree in the training process. Once the labels are binarized, the function applies a logical OR to the hyperglycemia column with the severe hyperglycemia columns. One example of this binarization is in Table 5.3.

However, the diagnosis of the current block is not the desired label to extract the patterns because the patient need to anticipate to a risk situation before suffering it. The desired label is one imminent risk situation that the patient can identify and take action to prevent it. This forthcoming risk situation is identified in the next block, which means at least two hours before of the next meal. This way, the patient can pay more attention to his

blood glucose values or change his habits for that day to avoid the potential risk.

The function aggregates the data in blocks with a logical OR in such a way that one single register with a positive diagnosis sets a positive diagnosis on the block. Then, the labels are shifted and each row has the label corresponding to the diagnosis of the following block.

5.4. Model training

The model is composed of three decision trees, one for each diagnosis and it uses the *DecisionTreeClassifier* class of the *scikit-learn* library (Pedregosa et al., 2011). Before training the model, the user has the possibility of specifying via parameters the features to be used in the training process. The classifier has many configurable parameters, some of them necessary to avoid the generation of complex patterns and avoid the overfitting.

The criterion used to make the splits is the Gini impurity rather than entropy in order to minimise misclassification probability (Ribas Ripol, 2013). However, the choice of impurity measures has little effect because they are quite consistent with each other. (Tan et al., 2006). This book also states that the splitting strategy has a greater impact than the impurity measure. The selected strategy to split at each node is to choose the best split rather than a random split. In this case, the best split is the one that minimises the Gini impurity of the children nodes.

Another important parameter that determines the quality of the patterns is the minimum number of samples required to split a node. This parameter is important because it allows stopping splitting those leaves that do not contain a significant number of samples and keep only the relevant patterns. By default, it is set to a 10 % of the total, but this is a parameter that can be configured by the user if he requires patterns with a higher number of samples. It means that all the extracted represent at least the 10 % of the data set.

The depth of the tree is another parameter that the application allows to configure (By default, is five). This parameter affects the number of rules that compose a pattern. The number of patterns may vary from zero (If the tree has only the root node) to the number of leaves. The algorithm stop splitting when all the leaves have no impurity, when all leaves contain less than the minimum of samples or when the maximum depth is reached. This parameter is quite useful because it allows the user to set the complexity of the patterns and increase their readability and comprehensibility. It also allows to avoid overfitting because very complex patterns may not be general enough to replay a future risk situation.

Other parameters enable to assign different weights to each feature, but this was not desired in this case because all the features are treated equally,

having the same possibility of becoming a relevant feature in the pattern. Therefore, the rest of the parameters were set to their default values. Figure 5.5 shows one decision tree that contains patterns of hyperglycemia.

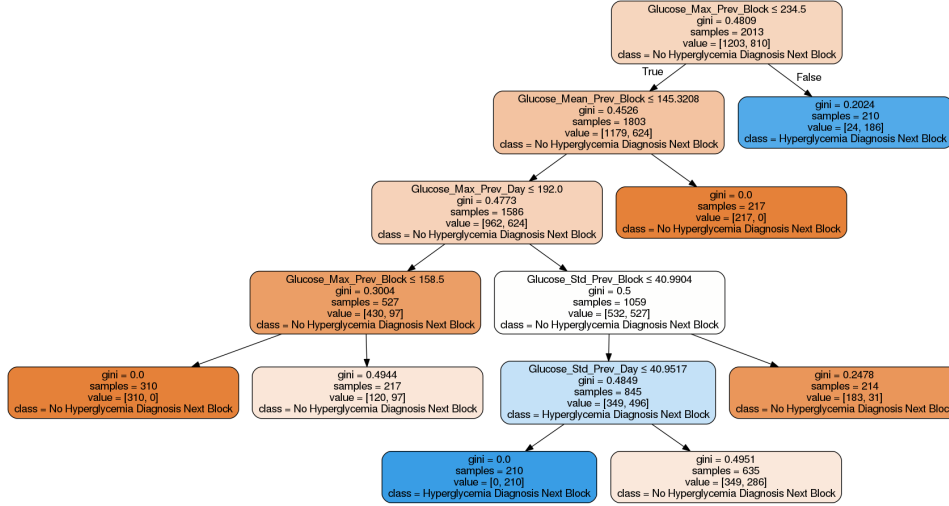


Figura 5.5: Decision tree that detects patterns of hyperglycemia. Nodes that correspond to risk situations are drawn in blue. Figure C.1 shows another example of a hyperglycemia tree

After fitting the decision trees with the training data and their corresponding labels, the model extracts the patterns from the tree. Recursively, one method traverses all the branches of the tree and keep all of them that has a positive label as a leaf (The class that corresponds to a risk situation). This function allows filtering those branches whose leaf has an impurity value greater than a threshold given by the user. The threshold set by default is 0.3, and if this threshold is reduced, only the purest patterns will be returned by the model, increasing the precision but reducing the recall.

Finally, the model builds a list of *Pattern* objects, composed of *Rule* objects. Each rule is composed of one feature, and operator and a threshold value. For example, a rule defined as $G < 180$ means that the current value of glucose must be lower than 180 mg/dL. The model contains an inner class to create compound rules when the same feature appears several times in the pattern, which increases the readability of the pattern. For example, if the rule $G \leq 180$ is contained in one node and $G > 135$ appears in one of its child nodes, it will be represented as a compound rule that contains one feature, two operators and two thresholds. The compound rule $135 \leq G < 180$ is translated as follows: The current value of glucose must be lower than 180 mg/dL and greater or equal than 135 mg/dL.

5.5. Report generation

The last step of the methodology is generating the report using the patterns extracted in the previous step together with some additional information obtained from the main dataset. The application uses an HTML template that is the backbone of the report, and the library *Jinja2* renders this template using a dictionary that contains the variables generated in Python. This template is completely dynamic, and its style and content can be customized just like a web page.

The method that generates the report accepts a parameter with the language of the report and configures the *Translator* object according to this parameter. Therefore, all the variables that the method passes to the template are previously translated, and the help page that is included at the end of the report also changes depending on the language. The method can generate the report in both PDF and HTML format. The images that appear the report (such as the tree graphs or the plots) are saved previously in a folder with a unique identifier provided as a parameter in case the user application wants to use them for other purposes.

The report is structured in four parts:

1. Information about the patterns along with their rules for each risk situation
2. Decision trees that have been used to obtained the patterns
3. Statistics and division in blocks of every day in the data set
4. Information about the contents of the report

The warnings issued by the application core are displayed at the beginning of the report. For example, if the quality of the dataset is not sufficient, a message alerts the patient that the patterns may not be accurate. After these warnings, the first part contains the patterns of hyperglycemia, hypoglycemia and severe hyperglycemia. If it has not been possible to obtain patterns for any of these conditions, the report does not include the section of patterns for that condition. The following elements compose each pattern:

1. Set of rules that describe the risk situation in the next block.
2. Number of samples of the data set that are obtained by the defined rules in the pattern together with the percentage of samples regarding the total of the data set
3. Impurity of the pattern.
4. Positive samples classified as a risk situation in the next block along with the percentage of samples regarding the total of positive samples

5. Negative samples classified as a situation without risk in the next block along with the percentage of samples regarding the total of negative samples.

The second part of the report shows the graphical representation of each tree. These images provide additional information that cannot be obtained from the patterns. The trees show all the patterns, including the ones that do not define a risk situation. The colour scale of each node determines both the majority class and the impurity. The colours of the tree are a good indicator to identify if the patient tends to suffer from a condition more than another. For example, in Figure 5.6, it can be observed that the patient tends to suffer from hypoglycemia at least one time in each block.

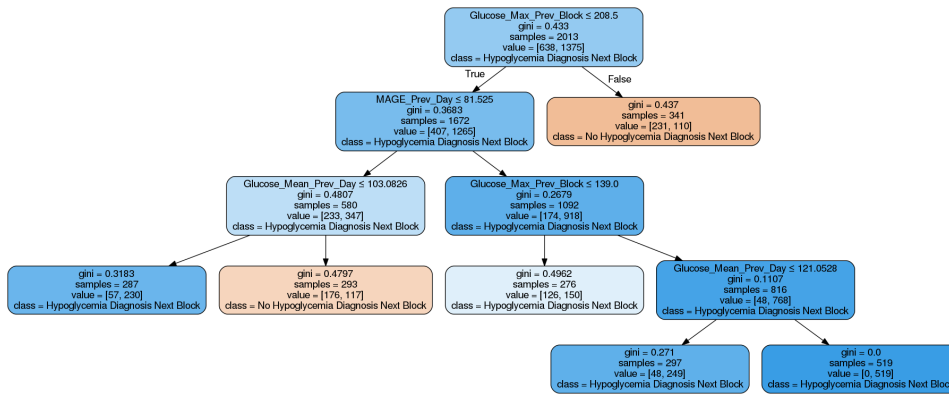


Figure 5.6: Decision tree that detects patterns of hypoglycemia. Nodes that correspond to risk situations are drawn in blue. Figure C.2 shows another example of a hypoglycemia tree

The intensity of the colour increases as the impurity of the node decreases. It means that the patterns that end in a leaf with an intense colour (either blue or orange) are the ones that are capable of separate samples that only belongs to one class. Also, each node also indicates its impurity value, the number of samples that follow its rule, the number of samples that belongs to each class and the majority class (which determines the label of the node).

The third part of the report is optional and appears in the report only if the user passes a certain parameter. This information can help the patient or physician to see where the decisions of the tree come from and see the blocks that usually lead to a risk situation. It includes statistics per block and day such as the maximum and minimum, mean and standard deviation of the blood glucose values and the glycemic variability measured with MAGE.

Finally, the fourth part is just information that helps the patient and the physician to understand the concepts that are detailed in this document

and makes each report a self-contained piece of information. In Appendix B, there is a sample of a generated report containing all the patterns, the information of the blocks of one day and the information about the report.

Chapter 6

Experimental results

Ten patients provided twelve different data files for developing and testing the application. The mean age of the patients was 34 years with a standard deviation of 10.34. Regarding their height, the patients had an average height of 165 cm with a standard deviation of 9.12m. Finally, their weights values had a mean of 66.11 kg with a standard deviation of 16.75 kg.

Two of the data files provided by these patients did not contain any register of carbohydrates (Register type 5), and the application returned an error because no block could be defined. The ten remaining files contained a broad range of rows from 427 to 11444 and a mean of 2668,2 rows. There is no a perfect positive correlation between the number of days and the number of rows because some of the data files contained time gaps. These time gaps were produced if the patient did not synchronise the sensor with the device at any moment in a period of eight hours (As it was described in Section 5.2.1). These gaps also vary in a wide range of time from 8 hours to 2 weeks. The minimum period is four days; the maximum is 152 days, and the mean is 39,9 days.

Seven out of ten files produced a warning by the application, which reported that they had an average of less than three registers of carbohydrates per day. This warning may be considered as an indicator of the quality of the datafiles and, consequently, the quality of the generated patterns. Some of the features calculated from the data rely on the carbohydrates information entered by the patient such as the blocks or the minutes since the last meal. If this information is incomplete or faulty, the generated patterns also are likely to be imprecise. The patients that provided a high-quality data files were ACN, CAA and MPA (The data file corresponding to the period 25/05/16 - 29/05/16).

The decision trees were analysed considering several parameters:

1. Number of patterns extracted

2. Percentage of samples regarding the total, and impurity of the pattern with the largest coverage. The coverage was defined as the proportion of samples that fulfilled the rules of the pattern.
3. AUC score of the decision tree using 5-fold cross validation.
4. The degree of importance of its features

AUC (Area Under Curve) measures the overall performance of a model and its values usually fall in a range from 0.5 to 1. The minimum value is obtained by a model that makes random predictions and the maximum value is obtained by a perfect classifier. Values lower than this range indicates that the model performs worse than a random classifier (Hernandez et al., 2006). AUC metric is derived from the ROC (Receiver Operating Characteristic) plot and it is the most common quantitative index that describe it (Hanley y McNeil, 1982). This curve shows the relation between the true positive rate and the false positive rate as its discrimination threshold varies.

K -Fold cross validation splits the data set into k subsets (folds) of approximately equal size. After splitting the data set, the model is trained k times rotating $k-1$ folds and validating over the remaining fold (Kohavi et al., 1995). This evaluation was done using the AUC metric and rotating over five folds of each data set for this project. An existing implementation of cross-validation is provided by the method *cross_val_score* included in the package *model_selection* of the *sklearn* library.

The importance of the features of each tree is calculated using the Gini importance. (Breiman, 2015). The Gini importance of a feature is computed as a normalised total reduction of the Gini index in each split done considering the feature. The higher the Gini importance is, the more informative is a feature. After computing the importance of each feature in each tree for all the data sets, the results were grouped by the mean of the importance of the features for each type of tree. Figure 6.1 shows a summary of the importance of all the features.

All the decision trees that detected patterns of hyperglycemia provided at least one pattern with zero impurity. The largest patterns had a coverage average of 40,86 % and detected a mean of 1,8 patterns for all the data files. Two of the ten hyperglycemia decision trees did not provide any pattern, and the ones that provided only one pattern, it had a high coverage (71,08 and 67,66 %). The mean AUC score of the eight trees that produced at least one pattern was 0,6703, with a maximum of 1 and a minimum of 0,4186. It is relevant to highlight that the tree that scored an AUC of 1 was obtained using a data file that contained only 427 rows and a mean of more than three carbohydrates entries per day.

The most relevant feature of the hyperglycemia decision trees was max_{B-1} , with an average value of 0,1552. With similar values, there were other features related the blood glucose values of the patient such as μ_{D-1} and σ_{B-1}

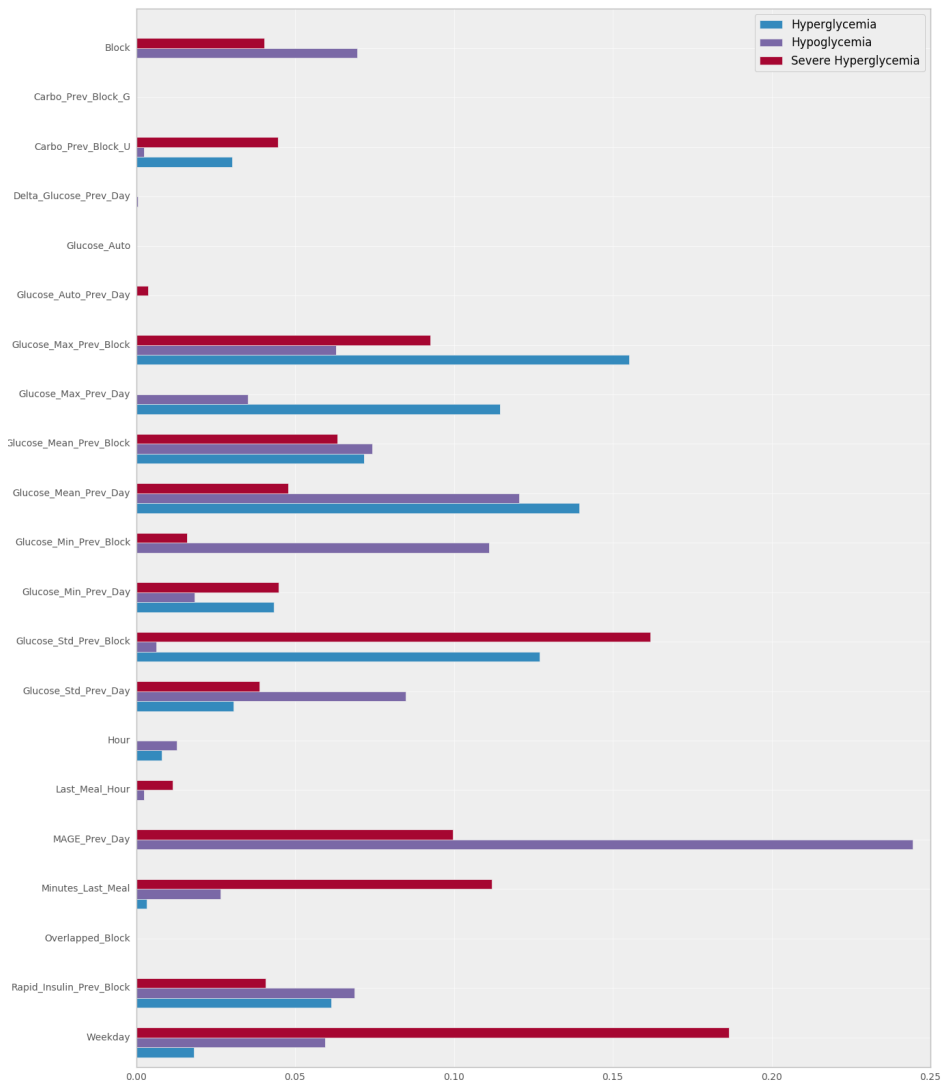


Figura 6.1: Average Gini importance of each feature for the three types of decision trees, obtained after processing ten different data sets.

Patient	Dates	Number of patterns	Samples (%) of the pattern with more coverage	Impurity of the pattern with more coverage
ACN	31/03/16 - 14/04/16	2	10,43 %	0
APD	20/06/16 - 04/07/16	0	-	-
APD	06/07/16 - 20/07/16	2	34,24 %	0
CAA	07/09/16 - 22/09/16	3	30,13 %	0
DPE	20/05/16 - 03/08/16	1	67,66 %	0
DSG	30/01/16 - 30/06/16	3	38,76 %	0
MPA	04/04/16 - 27/04/16	3	50,19 %	0
MPA	25/05/16 - 29/05/16	1	71,08 %	0
SBF	04/04/16 - 08/04/16	0	-	-
VGO	30/03/16 - 22/06/16	3	24,40 %	0

Table 6.1: Information about the decision trees focused on detecting hyperglycemia patterns.

with average values of 0,1395 and 0,1270. The following set of features were not used in any of the trees to describe a pattern:

$$\{B, car_{B-1}, \Delta G_{D-1}, G, G_{D-1}, min_{B-1}, H_{LM}, MAGE_{D-1}, OL_B\}$$

Regarding the hypoglycemia trees, all of them produced at least one pattern. The maximum coverage of a pattern was 63,38 %, with no impurity. The average of detected patterns 1,8, just as hyperglycemia decision trees. The mean AUC score of the trees was 0,6197, lower than the hyperglycemia trees with a maximum score of 1 and a minimum of 0,2834. The tree that scored the maximum score also was produced by a file with a low number of rows (407).

The most relevant feature of the hypoglycemia decision trees was $MAGE_{D-1}$, with a value of 0,2443. The second and third most importance features were μ_{D-1} and min_{B-1} , with average values of 0,1206 and 0,1110. It is relevant the difference between the primary feature and the second most important: the value of the first one is twice as high as the second one. $MAGE_{D-1}$ also had the highest value of Gini importance of all the trees, which means that is the most informative feature to describe a pattern (of hyperglycemia in this case). The set of the following features had an average Gini importance of 0: $\{car_{B-1}, G, G_{D-1}, OL_B\}$

The decision trees focused on detecting severe hyperglycemia patterns recognized patterns in seven cases, with a mean of 1,1 patterns, lower than the hyperglycemia and hypoglycemia decision trees. The mean AUC score

Patient	Dates	Number of patterns	Samples (%) of the pattern with more coverage	Impurity of the pattern with more coverage
ACN	31/03/16 - 14/04/16	2	25,78 %	0
APD	20/06/16 - 04/07/16	1	63,38 %	0
APD	06/07/16 - 20/07/16	2	17,52 %	0
CAA	07/09/16 - 22/09/16	2	10,42 %	0,1728
DPE	20/05/16 - 03/08/16	3	29,05 %	0
DSG	30/01/16 - 30/06/16	3	35,49 %	0
MPA	04/04/16 - 27/04/16	2	40,36 %	0
MPA	25/05/16 - 29/05/16	1	44,58 %	0
SBF	04/04/16 - 08/04/16	1	58,59 %	0
VGO	30/03/16 - 22/06/16	1	18,62 %	0,1653

Table 6.2: Information about the decision trees focused on detecting hypoglycemia patterns.

was close to the hyperglycemia decision trees score (0,6774), with a maximum of 1 and a minimum of 0,4463. The decision tree that scored the maximum AUC used the same data file that the decision tree of hyperglycemia that scored the maximum AUC, which contained the lowest number of rows of all the data files. The average coverage of the patterns was 31,81 %, lower than the other two types of decision trees.

The most informative feature of the patterns of severe hyperglycemia was WD , with a value of 0,1865. The second and third features in the ranking were σ_{B-1} and Δt_{LM} with an average Gini importance of 0,1619 and 0,1120. The set of features that were not considered in any of the patterns is the following one: $\{car_{B-1}, \Delta G_{D-1}, G, max_{D-1}, H, OL_B\}$

6.1. Results discussion

The coverage results indicated that the patients of the study either were prone to suffer further from hypoglycemia than hyperglycemia or that the hypoglycemia patterns can be described better by the features used by the decision trees. The first theory may follow the intuition that the diabetic patients that decided to participate in this study has a better control of their blood glucose values and therefore, a tendency to keep them low.

As it was expected, the coverage of the severe hyperglycemia patterns was lower than the ones produced by the hyperglycemia decision trees. This phenomenon happened because the number of positive cases of severe hy-

Patient	Dates	Number of patterns	Samples (%) of the pattern with more coverage	Impurity of the pattern with more coverage
ACN	31/03/16 - 14/04/16	0	-	-
APD	20/06/16 - 04/07/16	2	36,54 %	0
APD	06/07/16 - 20/07/16	1	19,19 %	0,2824
CAA	07/09/16 - 22/09/16	1	10,47 %	0,06479
DPE	20/05/16 - 03/08/16	2	38,00 %	0
DSG	30/01/16 - 30/06/16	2	19,72 %	0,1034
MPA	04/04/16 - 27/04/16	2	34,85 %	0
MPA	25/05/16 - 29/05/16	0	12,85 %	0
SBF	04/04/16 - 08/04/16	1	82,82 %	0
VGO	30/03/16 - 22/06/16	0	-	-

Table 6.3: Information about the decision trees focused on detecting severe hyperglycemia patterns.

perglycemia was a subset of the number of positive labels of hyperglycemia and consequently, their coverage should be lower or equal than the largest hyperglycemia pattern.

Furthermore, the results indicated a negative correlation between the number of rows and the AUC score. This negative correlation is more marked in severe hyperglycemia decision trees (-38,51) and can be appreciated in Figure 6.2. A possible explanation for this result may be that the data files with a low number of rows are biased due to their size and the patterns are easier to model than the ones with a higher sample size. Some studies like (Entezari-Maleki et al., 2009) showed that the AUC score of a single data set tends to increase when the sample size is larger.

However, in this case, we are comparing the score of decision trees that use data sets of different patients. Thus, the bias produced by the sample size and the quality of the carbohydrates entries has a high impact on the AUC score of the trees. It was not possible to establish a fair comparison between the AUC value of the decision trees of each patient because some variables such as the size of the data set, the number of carbohydrates entries and the number of gaps have a high variance in each of them. This negative correlation may not be a relevant result as the data files were not taken under the same circumstances and the data quality differs in each of them.

The analysis of the importance of the features led to several interesting conclusions. The first important result is the fact that hypoglycemia patterns used the glycemic variability of the previous day (MAGE) as the most informative feature. This phenomenon also appears in (Perea et al.,

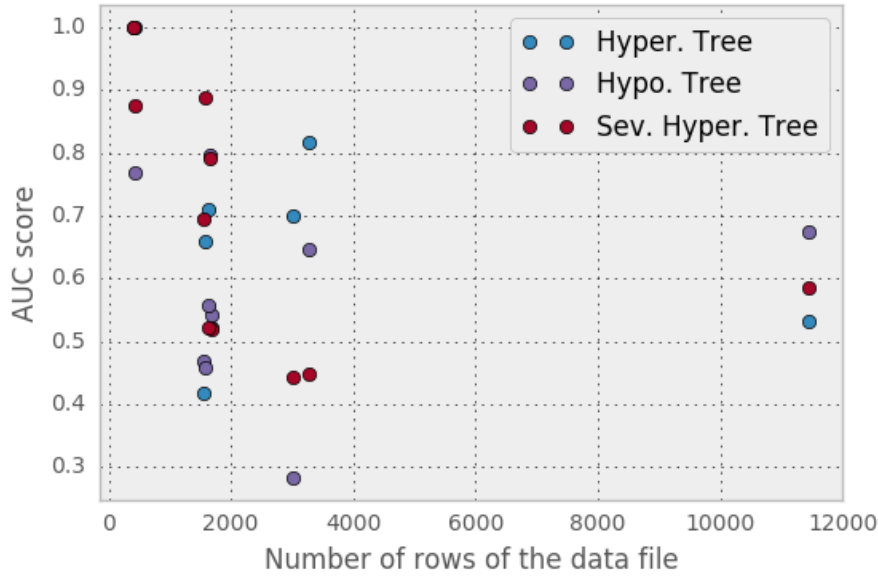


Figura 6.2: AUC score of the different decision trees and the number of rows of the provided data file.

2013), which states that MAGE was the only measure of glycemic variability significantly higher in the group of patients with repeated hypoglycemia.

The average Gini importance of $MAGE_{D-1}$ in hypoglycemia trees shows a contrast with the value obtained for hyperglycemia trees, where it was not used to do any split, resulting in a Gini importance of 0. This result has multiple possible interpretations, and it is an interesting topic to discuss. My hypothesis about this phenomenon is that patients who suffered a high glycemic variability the previous day tend to over-control their blood glucose values the next day, leading to hypoglycemia situations.

Another important result is that it does not exist a strong correlation between the importance of the features of hyperglycemia trees and severe hyperglycemia trees. Whereas the features that provide more information to the hyperglycemia trees were statistics related to blood glucose values, the decision trees focused on severe hyperglycemia used more the variables of time such as the day of the week or the minutes elapsed since the last meal to do their splits. This result may indicate that severe hyperglycemia situations can be more predictable by looking into the variables related to the lifestyle of the patient or the actions that are out of its routine. On the other hand, decision trees focused on detecting hyperglycemia situations should use blood glucose value to detect the risk situations rather than variables of time.

Lastly, some features were expected to be important because they provide values highly correlated with risk situations. For example, a patient who had a very low minimum of blood glucose the last block is more likely to suffer from hypoglycemia at any moment of the next blocks than a patient with a peak of blood glucose in the last meal. However, other features did not provide any information to the decision trees. These features were the current value of glucose, the difference of blood glucose with the previous day and the present value of blood glucose. These features were the current value of glucose, the difference of blood glucose with the previous day and the present value of blood glucose. This lack of importance suggests that considering one single value of blood glucose does not provide information gain to the trees and it is necessary to consider statistics and indicators that apply to a series of blood glucose values to increase their predictive power.

Chapter 7

Conclusions and future work

7.1. Conclusions

An application that applies machine learning techniques in its back-end sometimes suffers from a lack of transparency as it was difficult to track the origin of the provided results. A rigorous assessment of the medical advice given by these algorithms is essential to promoting the development of these applications and their use by patients and physicians. (Hart y Wyatt, 1990). Some questions about the use of black-box algorithms in decision-making support systems must be considered before they start to work in medical environments. The main feature of the application developed in this project is to be transparent to the user. The patient or physician can know about the origin of the patterns and use their criteria to either consider them valid or reject them.

The web application together with the core is ready to be tested with real data and be deployed to a production environment after considering some security issues that involves data protection and resilience to cyber attacks. Despite the limitations, all the requirements defined at the beginning of the document has been fulfilled, and the application can obtain some patterns that are potentially significant if the quality of the data source is good.

Thanks to this project, we have improved our programming skills using Python, and we have learnt Django to develop web applications using this programming language. Our knowledge about some machine learning techniques such as decision tree learning also has increased. This project has revealed us the potential of using and process the available data to raise the living standards of people that suffer from health conditions.

Carrying out a data science experiment is challenging because it is hard to estimate if the results are going to be useful or significant at early stages of the development process. This risk is inherent to a data-driven approach because the data do not always contains all the information needed for offer an appropriate service to the end user. This methodology seemed to worked

in this project as the final application provides a service to the user, placing the data at the centre of the application. However, many improvements can be made in the application, which are discussed in the following section.

7.2. Future work

At the beginning of the project, we wanted to tackle the problem with an unsupervised learning technique and the use of clustering to detect the patterns of glycemia. However, this technique was reconsidered as a supervised learning task to try to predict a future risk situation in the blood glucose values of the patient. The idea of dividing each day of the patient in blocks, defined by the ingestion of carbohydrates, can be used to generate new features and develop an online predictive tool in future projects.

One limitation of the application is that the patterns are not extracted in real time, but the patient needs to upload the file to a web application to obtain the results. This limitation is also present in the FreeStyle Libre application, which requires a connection from the reader to a computer through a USB cable. This project has suggested a way of detecting patterns, but the algorithm and the features can be modified to turn the model into a powerful predictive tool in real time. There are several machine learning techniques based on decision trees that use ensemble methods to obtain a better predictive performance.

One example of an ensemble classifier is random decision forest, which uses a multitude of decision trees, capable of mitigating the distortion caused by the existence of noise in the data set or reduce the overfitting of the model. Another example of an ensemble technique is the gradient tree boosting, which makes use of decision trees as base learners and distribute the weights to identify the trees capable of identifying the most intricate patterns. These ensemble models have a better performance than a single decision tree but it reduces the transparency of the model. Thus, they broke the constraint of this project of creating a transparent model, and they were not used to detect the patterns.

Another improvement can be done in the feature engineering process. The application only makes use of the features that are available to the physician or the patient and give him freedom of choosing which features are the ones he wants to use to discover new patterns. If the purpose of the model is to predict a future risk situation by using all the features it has at its disposal, tens of features can be extracted from time series. Also, many libraries are capable of making an automatic extraction of features from a time series. An example of this library is *tsfresh*, whose algorithm is described in (Christ et al., 2016). This library extracts up to 100 features from a time series in parallel and makes feature selection of the most relevant ones.

Some parts of the code, especially the generation of the report, can speed up by parallelizing its execution. Python has many libraries to make parallel computing like Dask. This library allows optimising an application using dynamic task scheduling and multicore execution. The application could offer a better experience to the patient if the time to generate the report is reduced and this is an excellent opportunity for improvement.

Finally, using the features of the data set, it is possible to define alternatives labels to discover new patterns. Two examples of possible phenomenons that can be analysed using the data obtained from FreeStyle Libre are the Dawn phenomenon and the Somogyi effect (This last one is well described in (Stephenson y Schernthaner, 1989)). The Somogyi effect consists on a rise of the blood glucose levels as a reaction of the body to a situation of nocturnal hypoglycemia, resulting in high blood sugar levels in the morning. The model could be adapted to detect if a patient suffers from this effect and report it so that his physician can provide him with some advice to avoid it.

Chapter 8

Conclusiones y trabajo futuro

8.1. Conclusiones

Una aplicación que aplica técnicas de aprendizaje automático en su *back-end* a veces sufre de una falta de transparencia que sería difícil rastrear el origen de los resultados devueltos. Una evaluación rigurosa del consejo médico dado por estos algoritmos es esencial para promover el desarrollo de estas aplicaciones y su uso por pacientes y médicos (Hart y Wyatt, 1990). Algunas preguntas sobre el uso de algoritmos de caja negra en sistemas de apoyo a la toma de decisiones deben ser consideradas antes de que empiecen a trabajar en entornos médicos. La característica principal de la aplicación desarrollada en este proyecto es ser transparente al usuario. El paciente o médico puede saber el origen de los patrones y usar su criterio para considerarlos o rechazarlos.

La aplicación web junto con el núcleo está preparada para ser probada con datos reales y desplegada en un entorno de producción des pues de considerar algunos aspectos sobre seguridad que implican protección de datos y resistencia a ciberataques. A pesar de las limitaciones, todos los requisitos definidos al principio del documento han sido cumplidos, y la aplicación puede obtener patrones que son potencialmente significativos si la calidad de los datos de origen es buena.

Gracias a este proyecto, hemos mejorado nuestras habilidades de programación usando Python, y hemos aprendido Django para desarrollar aplicaciones web usando este lenguaje de programación. Nuestro conocimiento sobre técnicas de aprendizaje automático tal como el aprendizaje con árboles de decisión también ha aumentado. Este proyecto nos ha revelado el potencial de usar y procesar los datos disponibles para mejorar los niveles de vida de las personas que sufren de alguna enfermedad.

Llevar a cabo un experimento de ciencia de datos es exigente porque

es difícil estimar si los resultados van a ser de utilidad o significativos a etapas tempranas del proceso de desarrollo. Este riesgo es inherente a una aproximación enfocada en los datos porque no siempre contienen toda la información necesaria para ofrecer un servicio adecuado al usuario final. Esta metodología creemos que funcionó en este proyecto ya que la aplicación final provee un servicio al usuario, situando los datos en el centro de la aplicación. Sin embargo, es posible hacer varias mejoras en la aplicación, las cuales son discutidas en la siguiente sección.

8.2. Trabajo futuro

Al principio del proyecto quisimos atajar el problema con una técnica de aprendizaje no supervisado y el uso de *clustering* para detectar los patrones de glucemia. Sin embargo, esta técnica fue replanteada como una tarea de aprendizaje supervisado para tratar de predecir una situación de riesgo futura en los valores de glucosa en sangre del paciente. La idea de dividir cada día del paciente en bloques, determinados por la ingesta de carbohidratos, puede ser usada para generar nuevas variables y desarrollar una herramienta *online* predictiva en futuros proyectos.

Una limitación de la aplicación es que los patrones no son extraídos en tiempo real, si no que el paciente necesita subir el fichero a la aplicación web para obtener los resultados. Esta limitación también está presente en la aplicación de FreeStyle Libre, que requiere una conexión desde el lector a un ordenador a través de un cable USB. Este proyecto ha sugerido una manera de detectar patrones, pero el algoritmo y las variables pueden ser modificadas para convertir el modelo en una poderosa herramienta de predicción en tiempo real. Hay varias técnicas de aprendizaje automático basadas en árboles de decisión que usan métodos ensamblados para obtener un mejor rendimiento en términos de predicción.

Un ejemplo de un clasificador ensamblado son los *bosques aleatorios*, que usan una multitud de árboles de decisión, capaces de mitigar la distorsión causada por la existencia de ruido en el conjunto de datos o reducir el sobreajuste del modelo. Otro ejemplo de una técnica ensamblada son los modelos *gradient boosting* basados en árboles de decisión, que usan dichos árboles como modelos de aprendizaje base y distribuyen los pesos para identificar los árboles capaces de identificar los patrones más complicados. Estos modelos ensamblados tienen un mejor rendimiento que un simple árbol de decisión, pero reducen la transparencia del modelo. Por este motivo, ellos no cumplían la restricción del proyecto de crear un modelo transparente, y no fueron usados para detectar patrones.

Otro proceso que puede ser mejorado es el de ingeniería de factores. La aplicación solo hace uso de variables que están disponibles al médico o al paciente y le dan la libertad de elegir que variables son las que desea usar

para descubrir nuevos patrones. Si el objetivo del modelo es predecir una situación de riesgo futura usando todas las variables a su disposición, decenas de variables pueden ser extraídas de una serie temporal. Además, muchas librerías son capaces de hacer una extracción automática de características de una serie temporal. Un ejemplo de esta librería es *tsfresh*, cuyo algoritmo es descrito en (Christ et al., 2016). Esta librería extrae hasta 100 características de una serie temporal en paralelo y hace selección de las variables más relevantes.

Some parts of the code, especially the generation of the report, can speed up by parallelizing its execution. Python has many libraries to make parallel computing like Dask. This library allows optimising an application using dynamic task scheduling and multicore execution. The application could offer a better experience to the patient if the time to generate the report is reduced and this is an excellent opportunity for improvement.

Finalmente, usando las características del conjunto de datos, es posible definir etiquetas alternativas para descubrir nuevos patrones. Dos ejemplos de posibles fenómenos que pueden ser analizados usando los datos obtenidos de FreeStyle Libre son el fenómeno del alba y el efecto Somogyi. (Este último es bien descrito en (Stephenson y Schernthaner, 1989)). El efecto Somogyi consiste en el aumento de los niveles de glucosa en sangre como una reacción del cuerpo a una situación de hipoglucemia nocturna, y que resulta en valores altos de azúcar por la mañana. El modelo podría ser adaptado para detectar si el paciente sufre de este efecto y avisarle para que su médico pueda proporcionarle algún consejo para evitarlo.

Appendix A

DecisionTreeClassifier example

The following code written in Python shows one example of how to use the libraries *sklearn* and *mlxtend* to train four decision trees and display the decision areas of the trees. This code has the purpose of studying the effect of varying the maximum depth constraint in the decision areas of each decision tree. The decision trees are trained to predict hyperglycemia and hypoglycemia situations using blood glucose values of the previous and subsequent registers. The resulting plots can be seen in Figure 3.2.

```
from sklearn.tree import DecisionTreeClassifier
from sklearn.model_selection import StratifiedShuffleSplit
import matplotlib.pyplot as plt
import matplotlib.gridspec as gridspec
5 from mlxtend.plotting import plot_decision_regions
import itertools
import pandas as pd

# Function that set the thresholds which define the labels
10 def label_map(value):
    hypoglycemia_threshold = 70
    hyperglycemia_threshold = 180
    if value > hyperglycemia_threshold:
        return 0
15 elif value < hypoglycemia_threshold:
    return 1
    else:
        return 2

20 # Read the FreeStyle data file in CSV format
file = "../data/ACN_20160331_20160414_FREE_STYLE.txt"
```

```

raw_data = pd.read_csv(file, header=0, skiprows=1,
                        delimiter="\t", index_col=0,
25      usecols=list(range(0, 9)),
                        parse_dates=['Hora'], decimal=".",
                        date_parser=
                        lambda x: pd.to_datetime(
                            x, format="%Y/%m/%d %H:%M"))
30
# Keep only registers of type 0 (Automatic blood
# glucose measurement)
data = raw_data[
    raw_data["Tipo de registro"] == 0][
35    ["Hora", "Historico glucosa (mg/dL)"]
    ].set_index(
        "Hora", drop=True)

# Create the input dataset with two columns resulting from
# shifting the column of blood glucose values +/- one period
40 X = pd.concat([data.shift(periods=-1), data.shift(periods=1)]
                ,axis=1).dropna()
X.columns = ["Glucose_Minus_15min",
             "Glucose_Plus_15min"]
45 y = data.loc[X.index].iloc[:,0].apply(label_map)

# Create the DecisionTreeClassifier objects with different
# max_depth
clf1 = DecisionTreeClassifier(criterion='gini',
50      splitter='best', max_depth=1)
clf2 = DecisionTreeClassifier(criterion='gini',
      splitter='best', max_depth=2)
clf3 = DecisionTreeClassifier(criterion='gini',
      splitter='best', max_depth=3)
55 clf4 = DecisionTreeClassifier(criterion='gini',
      splitter='best', max_depth=4)

# Get a stratified sample of training and test examples
# (80% Training - 20% Test)
60 sss = StratifiedShuffleSplit(n_splits=1, test_size=0.2,
                              random_state=0)
train_index, test_index = next(sss.split(X, y))
X_train, X_test = X.iloc[train_index], X.iloc[test_index]
y_train, y_test = y.iloc[train_index], y.iloc[test_index]
65

# Plot decision regions of the four decision trees
gs = gridspec.GridSpec(2, 2)
fig = plt.figure(figsize=(14, 14))
for clf, lab, grd in zip([clf1, clf2, clf3, clf4],
70      ['DT Max. Depth = 1',
        'DT Max Depth = 2',

```

```
        'DT Tree Max Depth = 3',
        'DT Tree Max Depth = 4'],
        itertools.product([0, 1], repeat=2)):
75     # Train the decision tree
    clf.fit(X, y)

    #Create a subplot with its decision region
    ax = plt.subplot(gs[grd[0], grd[1]])
80     fig = plot_decision_regions(X=X.as_matrix(),
                                y=y.as_matrix(),
                                clf=clf, legend=2)

    plt.title(lab)
    plt.xlabel('Blood glucose (mg/dL) -15min')
85     plt.ylabel('Blood glucose (mg/dL) +15min')
plt.show()
```


Appendix B

Report example

Report of patterns

ACN

31/03/16 - 14/04/16

Hyperglycemia patterns

Pattern 1

- Maximum level of glucose of the previous block is lower or equal than 234.5
- Mean level of glucose of the previous block is lower or equal than 145.3
- Maximum level of glucose of the previous day is greater than 192
- Standard deviation of the level of glucose of the previous block is lower or equal than 40.99
- Standard deviation of the level of glucose of the previous day is lower or equal than 40.95

Samples: 210 (10.43%)

Impurity: 0

Number of positive samples: 210 (25.93%)

Number of negative samples: 0 (0.00%)

Pattern 2

- Maximum level of glucose of the previous block is greater than 234.5

Samples: 210 (10.43%)

Impurity: 0.2024

Number of positive samples: 186 (22.96%)

Number of negative samples: 24 (2.00%)

Hypoglycemia patterns

Pattern 1

- Maximum level of glucose of the previous block is greater than 139 and is lower or equal than 208.5
- Glycemic variability (MAGE) of the previous day is greater than 81.53
- Mean of the level of glucose of the previous day is lower or equal than 121.1

Samples: 297 (14.75%)

Impurity: 0.271

Number of positive samples: 249 (18.11%)

Number of negative samples: 48 (7.52%)

Pattern 2

- Maximum level of glucose of the previous block is greater than 139 and is lower or equal than 208.5
- Glycemic variability (MAGE) of the previous day is greater than 81.53
- Mean of the level of glucose of the previous day is greater than 121.1

Samples: 519 (25.78%)

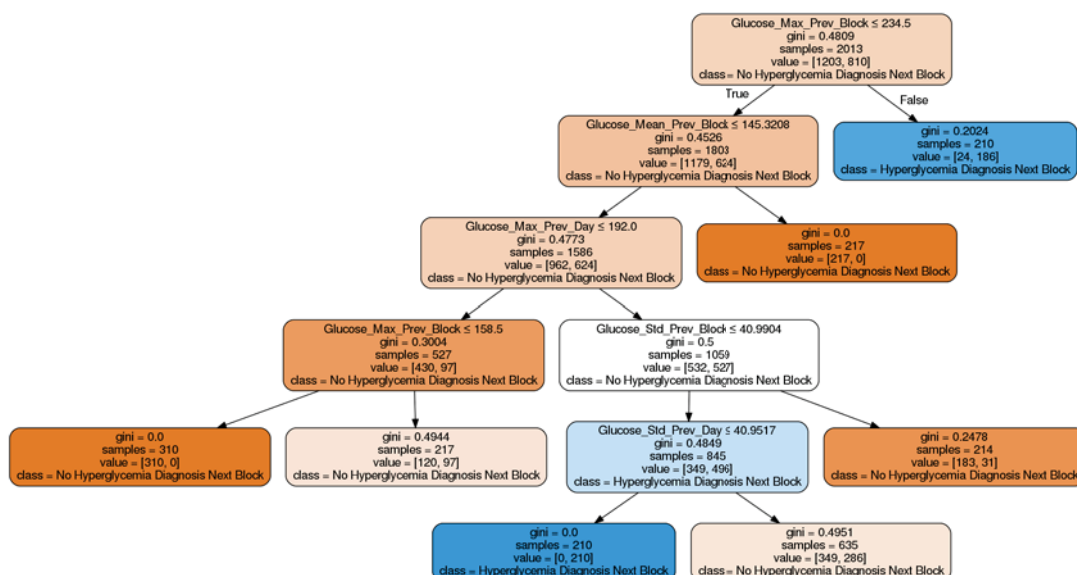
Impurity: 0

Number of positive samples: 519 (37.75%)

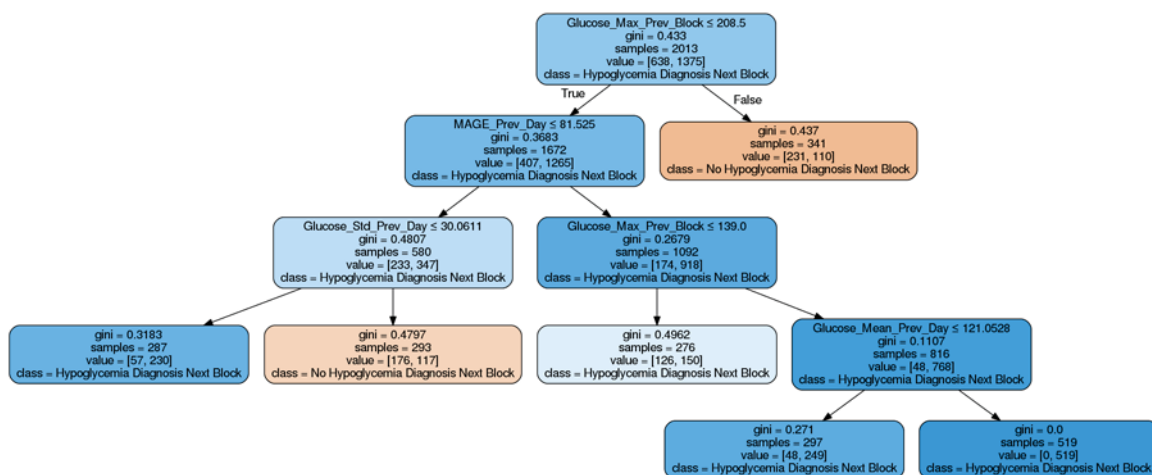
Number of negative samples: 0 (0.00%)

Decision trees

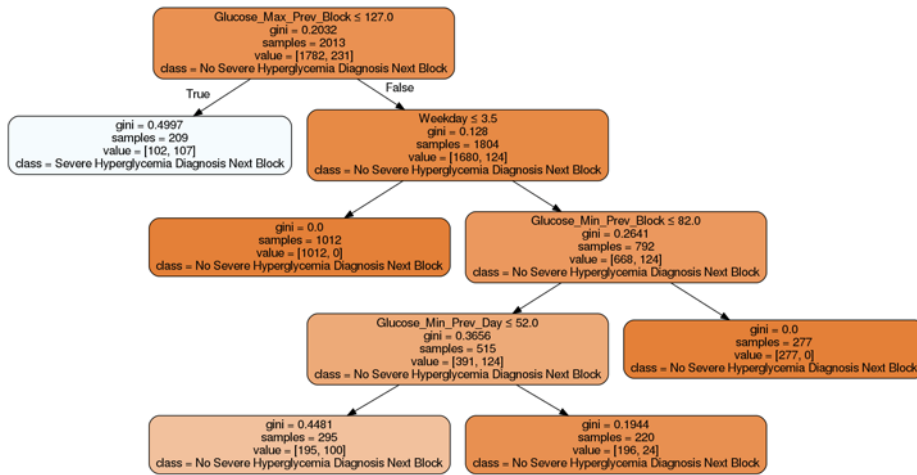
Hyperglycemia



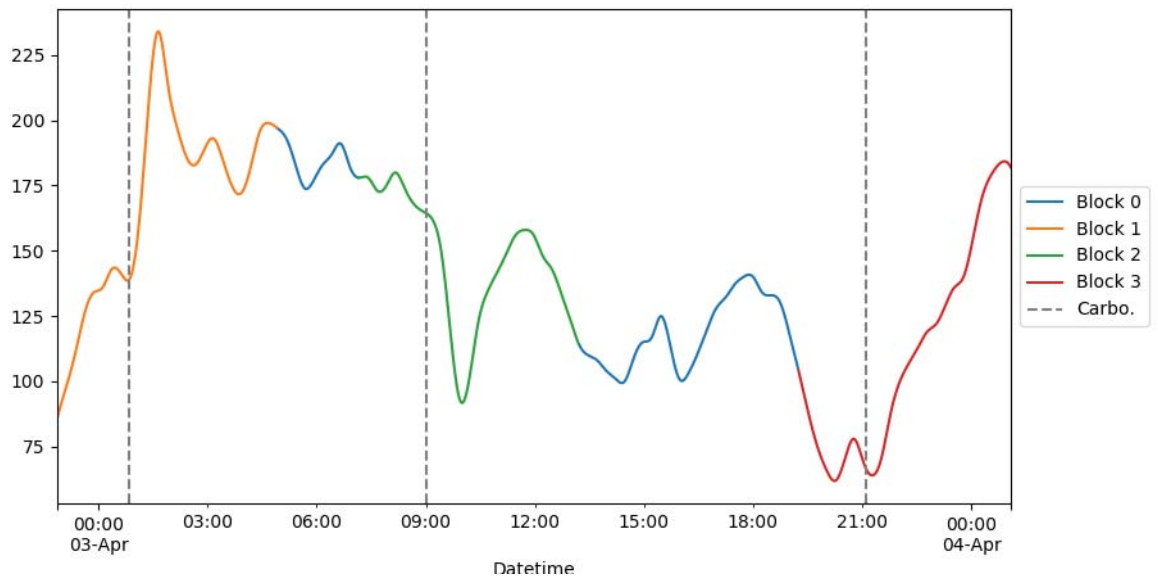
Hypoglycemia



Severe hyperglycemia



03/04/2016



Block	Carbohydrates (portions)	Rapid-acting insulin (units)	Glucose level statistics			
			Mean	Standard deviation	Maximum	Minimum
1	1	1	166.125	38.1454	234	86
0	0	0	136.697	32.3772	197	100
2	1	1	149.042	24.5737	180	93
3	1	1	111.292	40.5114	184	62

Day summary of glucose values

- Mean of the level of glucose of the day: 140.438
- Standard deviation of the level of glucose of the previous day: 38.8674
- Maximum level of glucose of the previous day: 234
- Minimum level of glucose of the previous day: 62
- Glycemic variability (MAGE): 76.4

Report information

What is a pattern?

A pattern is a set of rules that describe a situation in the patient's life using several metrics related to his glucose level, insulin values, carbohydrates and time variables. Through these rules, it is possible to identify risk situation with regard to the glucose levels of the patient.

What is a block?

Each day of the patient is divided in a series of blocks defined by the different meals that the patient has throughout the day. One block is defined by a time period that starts two hours before a meal and finishes four hours later. The blocks may be overlapped and include intakes of carbohydrates and insulin doses that are present also in other blocks. Block zero always corresponds to the remaining time that is not framed by any other block

What type of patterns are there?

The information that a pattern provides depends on its type. The patterns can be of three types: Hyperglycemia, hypoglycemia and severe hyperglycemia patterns. The patterns of each type describe situations when the patient suffers from a disorder in his glucose level in the next meal block. The thresholds that determine a risk situation are the following ones:

- Hyperglycemia: 180 mg/dL
- Hypoglycemia: 70 mg/dL
- Severe hyperglycemia: 240 mg/dL

What information does a pattern provide?

Each pattern is composed by the following elements:

1. Set of rules that describe the risk situation in the next block
2. Number of samples of the data set that are obtained by the defined rules in the pattern. Moreover, it is displayed the percentage of samples regarding to the total of the data set
3. Impurity of the pattern using Gini impurity. It reaches its minimum (zero) when all the samples obtained by the defined rules are classified as risk situation in the next block
4. Number of positive samples, classified as a risk situation in the next block. Moreover, it shows the percentage of samples regarding to the total of positive samples
5. Number of negative samples, classified as a situation without risk in the next block. Moreover, it shows the percentage of samples regarding to the total of negative samples

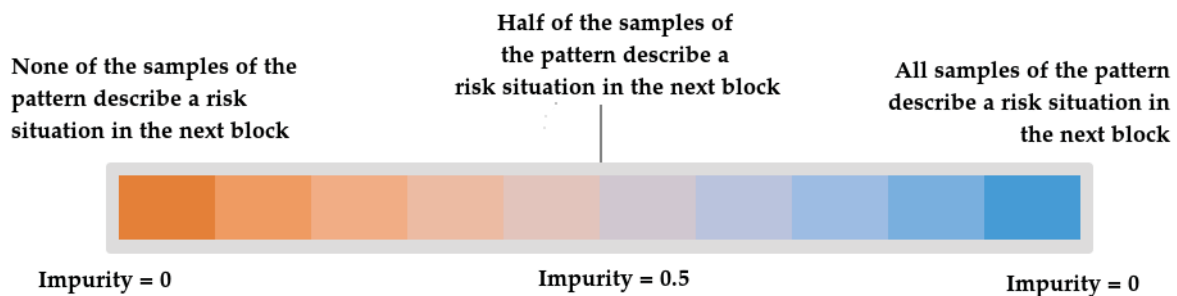
How to assess a pattern?

To assess a pattern it is necessary to consider two factors:

1. The number of samples must be relevant. The threshold of minimum samples is a 10% of the total, but this does not mean that it is the minimum number to consider a pattern as relevant. This criteria must be set by the patient or the physician.
2. The pattern does not have to have a minimal impurity. Long patterns with complex rules tend to overfit the model even though the maximum depth of the tree is set to 5 levels. This means that, although the pattern's impurity was close to zero, the model would be overfitted and not be accurate in future risk situations.

How to interpret a decision tree?

The decision tree contains both the patterns of a risk situation and the patterns of a situation with no risk. The nodes of the tree can be interpreted through their written information or their color. The color scale of each node determines both the majority class of the samples obtained by the split made in the parent node and how impure is the split. In the following color scale, it can be observed the impurity of the split according to the color intensity of each node:



Appendix C

Examples of decision trees

The next decision trees were generated using the data file provided by the patient CAA during the period between 07/09/2016 and 22/09/2016. The rest of the reports of the patients, which contain the decision trees, are available at the following link of Google Drive: https://drive.google.com/drive/folders/0Bw6PbR_m3nxNUS1XZlIwQ21QWDg

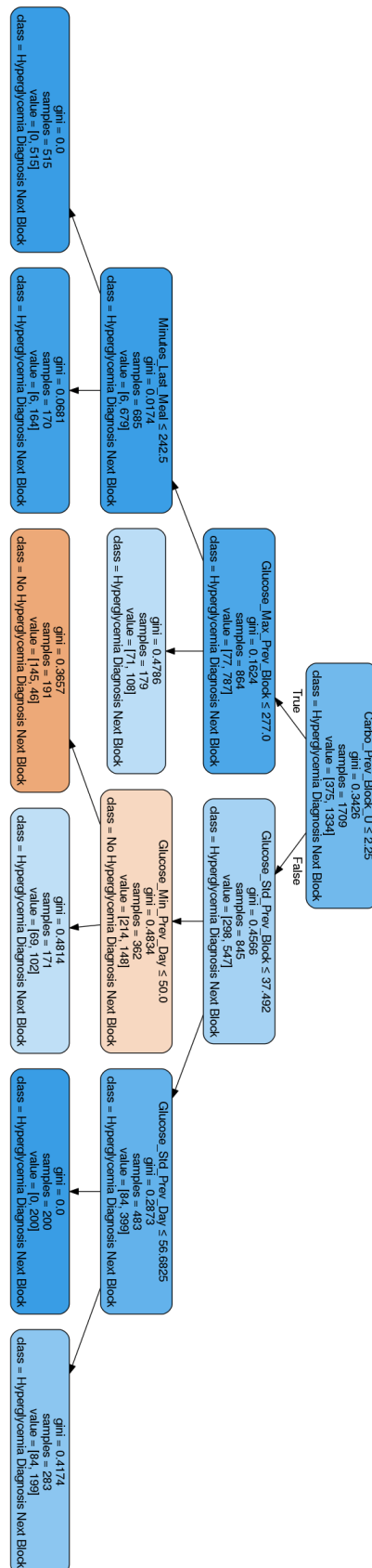


Figura C.1: Decision tree specialised in detecting patterns of hyperglycemia.

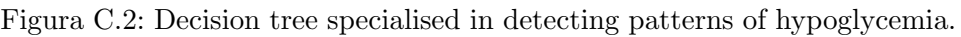


Figura C.2: Decision tree specialised in detecting patterns of hypoglycemia.

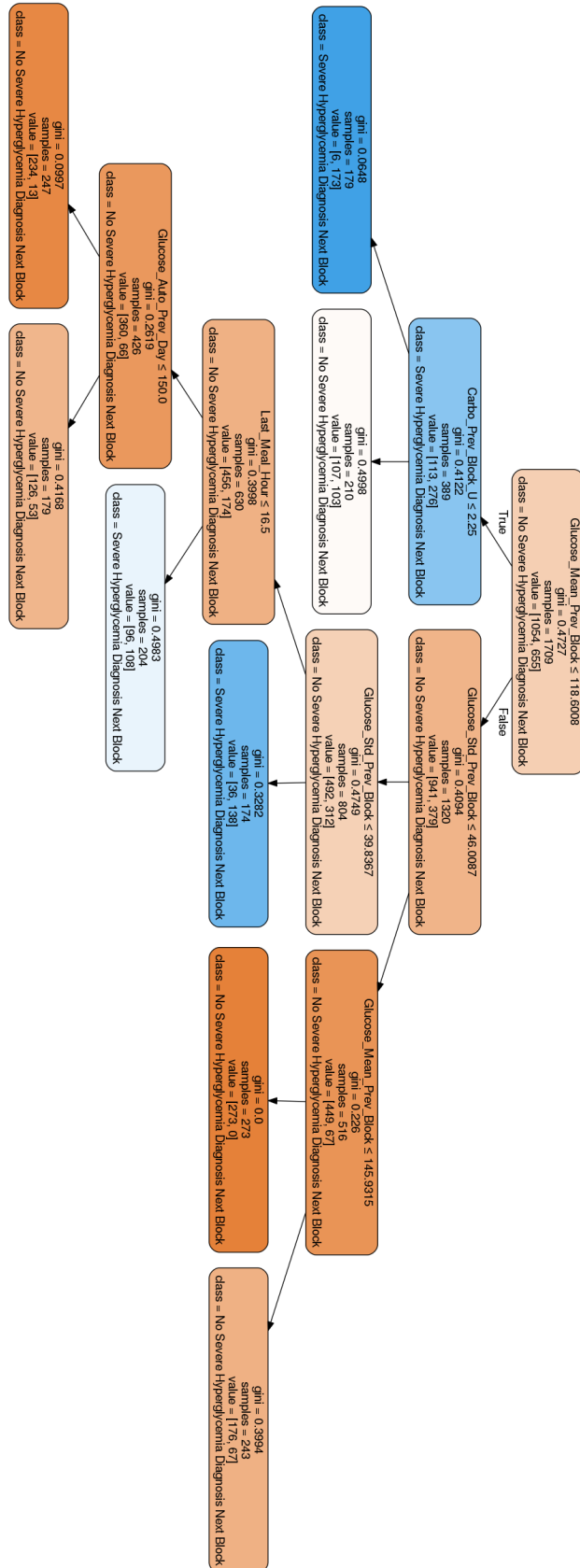


Figura C.3: Decision tree specialised in detecting patterns of severe hyperglycemia.

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